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Investigations into the synthesis of heterocyclic compounds with biological applications



A thesis submitted to Keele University in
partial fulfilment for the requirements for the
degree of Doctor of Philosophy in Chemistry

By

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Abstract

There is a growing body of literature that recognises the importance of tandem reactions, where a number of transformations are carried out in a one-pot process. Such reactions offer considerable benefits such as: a reduction in time, and the sequence of synthetic processes that subsequently improve in efficiency. Particularly useful is the one-pot cascade of transforming alcohols to alkenes using an Oxidation-Wittig sequence. Although, the Wittig reaction is a dominant and powerful olefination method, sometimes the isolation of, instability of, toxicity of, or volatility of the carbonyl compounds that are applied in a Wittig reaction is limiting. However, a tandem oxidation processes (TOP) in the presence of a number of oxidants can be employed to overcome these shortcomings. Herein, a variety of starting materials were used to construct six and five membered rings that possibly could be annulated later.

Chapter 2 describes the attempted development of novel methodology for the construction of carbon-carbon bonds from diols in two routes. Firstly, a domino oxidation-Wittig olefination reaction was attempted to convert diols into extended alkene products through reacting with different ylides. The electrocyclisation of those alkenes (trienes) has been examined using thermal and microwave irradiation. In the second route, work on the intramolecular annulation of alkenes *via* 6π -electrocyclisation and then oxidation is described. No ring closure was observed under thermal or photochemical promotion of the 6π -electrocyclisation.

The attempted application of acid-catalysed Nazarov reaction of divinyl ketones and TOP reaction of diol is described in **Chapter 3** using divinyl ketone **302** and dihydroxyacetone **294** as key intermediates but only limited success was achieved. The Nazarov cyclisation could not be promoted on the TOP derivatives obtained.

Chapter 4 explores the development of tandem oxidation/Diels-Alder reactions through potential inter- or intra-molecular Diels-Alder reactions. Firstly, two alcohols were used for the synthesis allyl and homo allyl esters *via* TOP reaction of cinnamyl alcohol and cyclohexenemethanol. Secondly, six vicinal diols and diketones were examined under the same conditions to synthesise dienes that might act as dienophiles. Unfortunately, no success was achieved.

The final chapter, describes the successful preparation, *via* Pictet-Spengler cyclisation, and evaluation of a number of novel 1,2,3,4-tetrahydro- β -carbolines that have anti-malarial activity. Although active, the compounds prepared did not show any significant increase in the growth inhibitory activity of compared to the existing collections, but they did successfully confirm the SAR model proposed.

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Huda

Abbreviations

¹³ C-NMR	¹³ C-Nuclear Magnetic Resonance
¹ H-NMR	¹ H-Nuclear Magnetic Resonance
Ac	Acetate
Boc	di- <i>tert</i> -butyl dicarbonate
cat.	catalyst
d	doublet
DCA	9,10-Dicyanoanthracene
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
dd	doublet doublet
ddt	doublet doublet triplet
DIBAL	Diisobutylaluminum hydride solution
DMAP	4-(Dimethylamino)pyridine
DMF	<i>N,N</i> -Dimethyl formamide
DMP	Dess-Martin Periodinane
DMSO	dimethyl sulfoxide
EDG	Electron Drawing Group
equiv.	equivalents
E ₁ cb	Elimination reaction
Et	Ethyl group
Et ₃ N	triethylamine
EWG	Electron Withdrawing Group
FMO	Frontier Molecular Orbital
h	hours
H ⁺	Acidic conditions
H ₂ SO ₄	sulfuric acid
HOMO	Highest Occupied Molecular Orbital
Hz	Hertz
IBX	Iodoxybenzoic acid
<i>J</i>	Coupling constant
LUMO	Lowest Occupied Molecular Orbital
μL	microliter
m	multiplet
M	Molar
Me	Methyl group
MeCN	acetonitrile
mmol	millimole
MTBD	(1-methyl-1,5,7-triazabicyclo[4,4,0]dec-5-ene)
MW	Microwave
<i>n</i> Bu	normal-Butyl
<i>n</i> -Bu ₂ O	normal-butyl oxide
NCS	N-chlorosuccinimide
NMR	Nuclear Magnetic Resonance
<i>o</i>	ortho
OTf	triflate

<i>p</i>	para
Ph	Phenyl group
q	quartet
rt	room temperature
s	singlet
SO ₃ Py	pyridine sulfur trioxide complex
S _N ¹ and S _N ²	Nucleophilic Substitution Reactions
t	triplet
<i>t</i> Bu	<i>tert</i> -butyl
TCNE	Tetracyanoethylene
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THβCs	Tetrahydro-β-carbolines
TIE	Tethered-Imine-Enamine
TLC	Thin layer chromatography
TOP	Tandem Oxidation Process
Ts	<i>p</i> -Toluenesulfonyl
UV	Ultraviolet
WHR	Woodward-Hoffmann Rules

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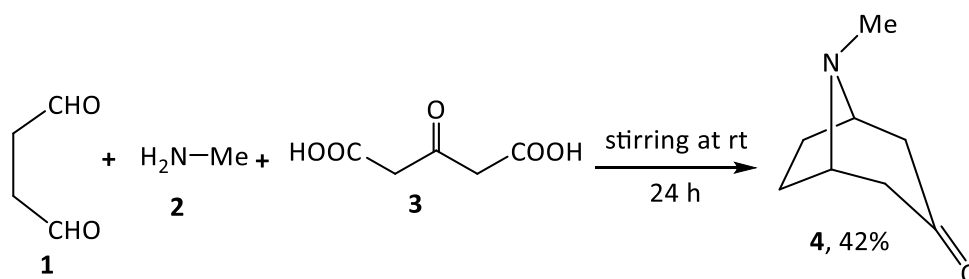
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Chapter 1 Introduction**1 Tandem reactions**

The past thirty years have seen increasingly rapid advances in the field of the development of novel tandem reactions. These reactions aim to create several bonds in a single process and can lead to the rapid construction of molecules, which are often complex. Synthetic chemistry has long searched for easy methods to synthesise complex organic molecules. A tandem reaction is a reaction in which several bonds are formed in sequence without isolating intermediates, changing reaction conditions, or adding reagents. Such methods are often referred to by different names like domino, cascade, sequential and 'zipper' that are all linked to performing multiple transformations in a single step.⁽¹⁾

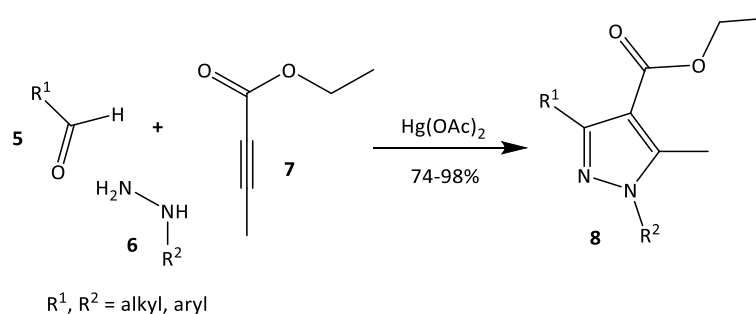
Ideally the development of tandem reaction methodologies could lead to many benefits; for example; a reduction in the amount of solvent waste, by-product waste produced and shorter reaction times.⁽²⁾ In addition to this, intermediates do not require purification and potentially higher yields can be obtained, when compared to stepwise processes. However, this ideal target is often impossible to achieve. These processes are important in both academia and industry, and ideally the synthesis of any target would proceed in the shortest number of steps from readily available starting materials. One of the earliest reported sequential reactions, a classic example of a domino reaction is Robinson's synthesis of Tropinone **4** in 1917. It reported that the combination of succinaldehyde **1**, methylamine **2** and 1,3-acetone dicarboxylic acid **3** afforded

tropinone **4**, using the Mannich reaction that includes the nucleophilic addition of an amine to a carbonyl group followed by dehydration step to give the Schiff base, as shown in Scheme 1.⁽³⁾



Scheme 1: Robinson's domino synthesis of Tropinone **4**

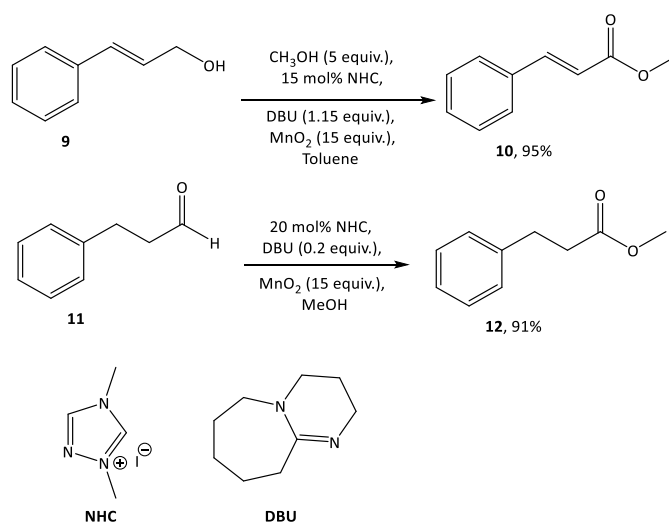
Significant improvements in tandem reactions are being reported daily. To provide a recent example, Bhadraiah and co-workers reported the synthesis of 1,3,4,5-tetra-substituted pyrazoles **8** rapidly and regioselectively in a one-pot, three-step sequence consisting of condensation, nitrilimine generation, and cycloaddition using mercuric acetate, as shown in Scheme 2.⁽⁴⁾



Scheme 2: Tandem reaction for synthesis substituted triazole

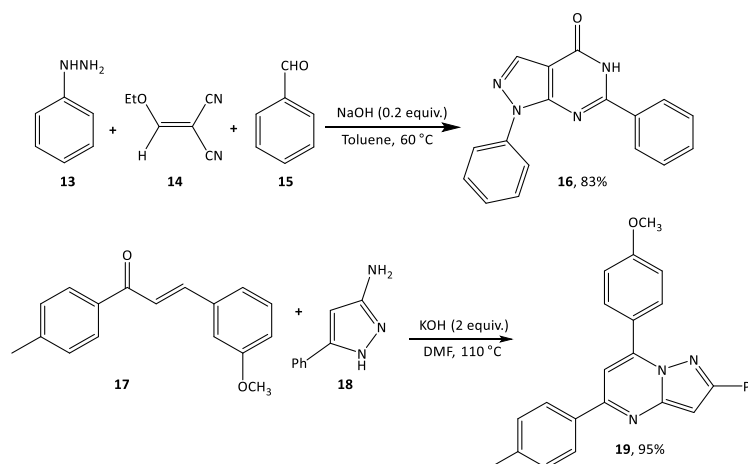
The use of tandem reactions is not however limited to synthesising rings. For example, Scheidt *et al* developed a one-pot process of tandem oxidation reaction of allylic and benzylic alcohols to esters **10**, and saturated aldehydes to saturated esters **12** using a simple triazolium salt as the pre-catalyst as

shown in Scheme 3.⁽⁵⁾ This is an example of how tandem reactions can also be used powerfully to accomplish otherwise challenging reactions.



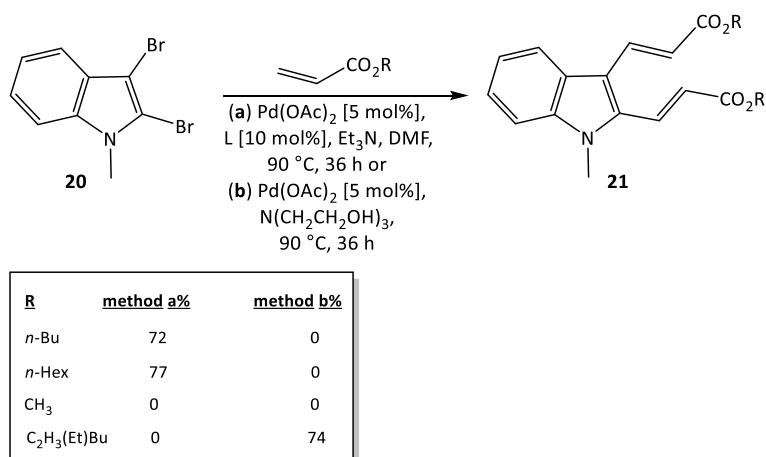
Scheme 3: Using catalysts to prepare esters **10** and **12**

Tandem reactions also do not always need expensive or complex catalysts. Liu *et al* (2016) developed an effective one-pot method for the synthesis of pyrazolo[3,4-d]pyrimidin-4-one **16** from the reaction of 2-(ethoxymethylene)malononitrile **14**, phenylhydrazine **13**, and benzaldehyde **15**.⁽⁶⁾ In addition, Kumar and co-workers used a potassium hydroxide mediated protocol to achieve the tandem cyclocondensation and rapid aromatization of 1H-pyrazol-3-amines and chalcones (Scheme 4). This protocol observed excellent improvement in yields. It was noted that the basicity and solubility of potassium hydroxide in DMF was responsible for these high yields, as shown in Scheme 4.^(7a)



Scheme 4: Using mild catalysts for the attempted tandem reactions

Palladium-catalysed Heck and cross-coupling reactions are a major area of interest within the field of synthetic organic chemistry.^(7b) Despite its long success, Pd-catalysed coupling reactions have a number of problems such as the growing requirement of starting materials and formation of halide salts waste. Langer *et al*⁽⁸⁾ reported twofold Heck reactions of 2,3-dibromo-N-methylindoles **20** with various acrylates, where it was proven as a successful reaction to synthesise the 2,3-di(alkenyl)indoles **21** from moderate to good yields, as shown in Scheme 5. These yields were obtained when it was carried out under Buchwald's conditions, using palladium (II) acetate [Pd(OAc)₂] and the biaryl monophosphine ligand in DMF. Alternatively for one substrate triethanolamine was used instead conveniently replacing the base, ligand, and solvent for the Heck reaction.



Scheme 5: The synthesis of 2,3-di(alkenyl)indoles **21** using Pd-catalysed coupling reaction

1.1 Classification of tandem reactions:

Chemists have classified tandem reactions into three groups.⁽¹⁾ The first is “sequential” reactions in which additional reagents must be added in order for the second reaction to occur, secondly, “consecutive” reactions in which another reagent is added after the first transformation without isolation of the first formed product and finally, “cascade or domino” reactions in which all reactions take place without the need for additional reagents or a change in reaction conditions (Scheme 6).



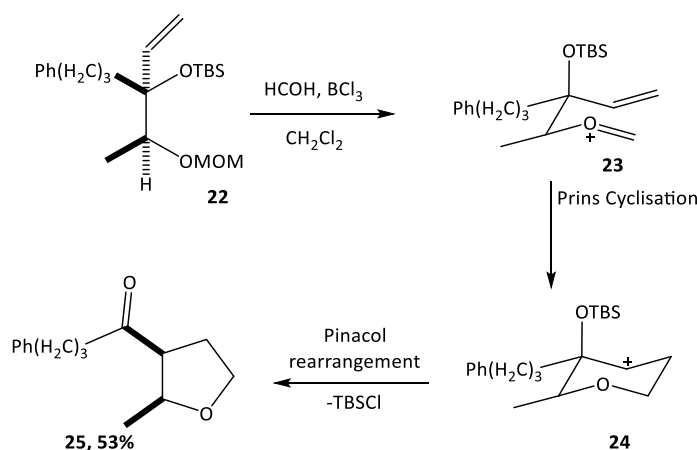
A and B = Reactants R = additional reagent [E] = Intermediate C and F = products

Scheme 6: Illustration of tandem reactions

Domino reactions themselves can be classified according to the basis of the steps involved. Electrophilic, nucleophilic, pericyclic, radical, and transition metal catalysed processes have been grouped by Nicolaou and co-workers (2006).⁽⁹⁾ In contrast, Tietze classifies these domino reactions into cationic, anionic, radical, pericyclic, photochemical, oxidative or reductive, and transition-metal induced transformations.⁽¹⁾

1.1.1 Cationic tandem reactions

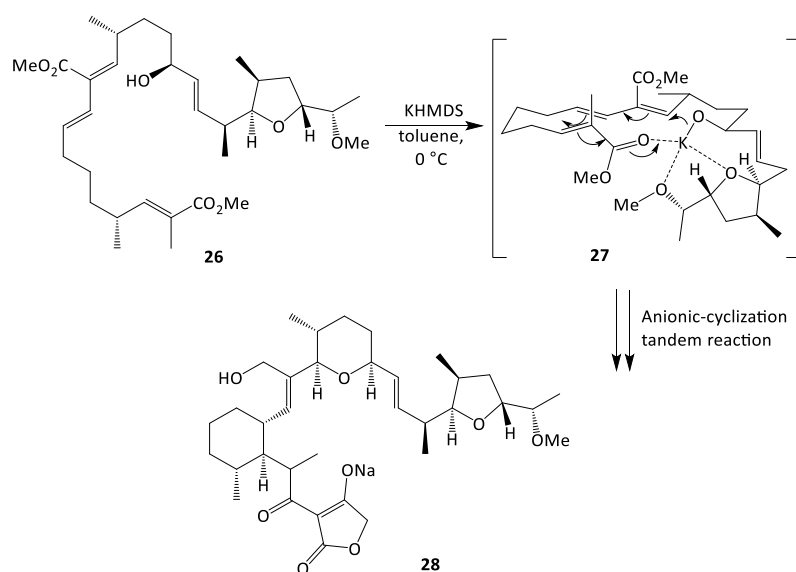
Cationic tandem reactions are considered the oldest known tandem reactions. A carbocation is generated either by elimination or by addition of a proton. Further reaction of the carbocation then produces a new carbocation.⁽¹⁰⁾ The development of cationic tandem reactions has played an extensive role in the synthesis of natural products. An excellent example of cationic reactions is the synthesis of 3-acyl-5-substituted tetrahydrofurans, prepared from methoxymethyl (MOM) or (methylthio)methyl (MTM) derivatives of allylic diols with good to moderate yields. However, Overman demonstrated that the functionality and stereochemistry of Lewis acid-promoted pinacol can be useful in this reaction to construct different oxacyclic products, depicted in Scheme 7.⁽¹¹⁾



Scheme 7: Lewis acid-promoted pinacol-terminated Prins cyclisation

1.1.2 Anionic tandem reactions

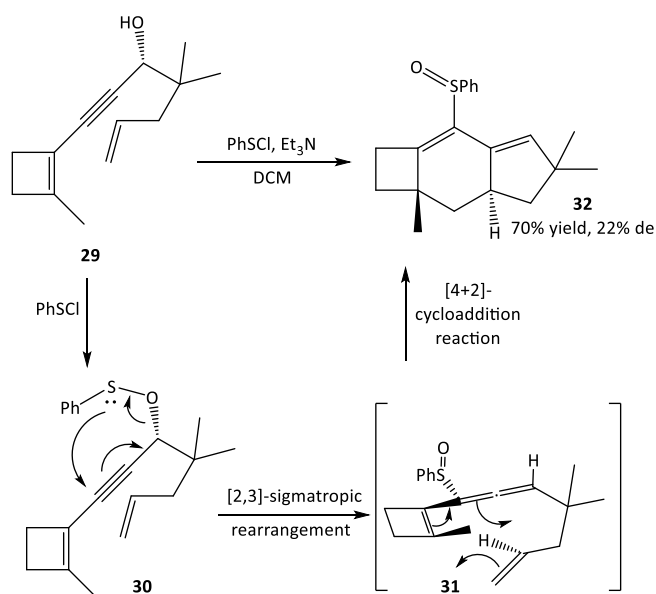
Anionic tandem reactions are also common in the literature. Carbanion formation involves a deprotonation of a CH group, and then this carbanion will attack an electrophile to create an anion that reacts with another electrophile to complete the desired reaction. There are a wide range of examples that include anionic–anionic processes like Michael-initiated or -terminated process. These examples are particularly utilised in organic syntheses.⁽¹²⁾ An elegant example of an anionic-cyclisation domino reaction is Ley's synthesis of tetronasin **28**, which is of commercial importance as an antibiotic, antiparasitic, and growth-promoting agent for ruminants. Reaction of **26** with potassium hexamethyldisilazide (1.1 equiv.) in toluene at 0 °C, afforded tetronasin **28** in 67% yield as a single diastereoisomer, the key step being a domino-cyclisation to proceed *via* potassium salt **27** (Scheme 8).⁽¹²⁾ A large number of other anionic tandem reactions in various synthetic contexts have been reported with undeniable benefits.⁽¹³⁻¹⁵⁾



Scheme 8: An anionic-cyclisation cascade in the synthesis of tetronasin **28**

1.1.3 Pericyclic tandem cascades

Many tandem routes to afford natural compounds targets, make use of pericyclic reactions, including cycloadditions, sigmatropic rearrangements and electrocyclic reactions. Gibbs and Okamura (1988) showed the total stereochemistry of the (+)-sterpurene (**32**, Scheme 9) through asymmetric tandem [2,3]-sigmatropic shift and intramolecular Diels-Alder reaction.⁽¹⁶⁾



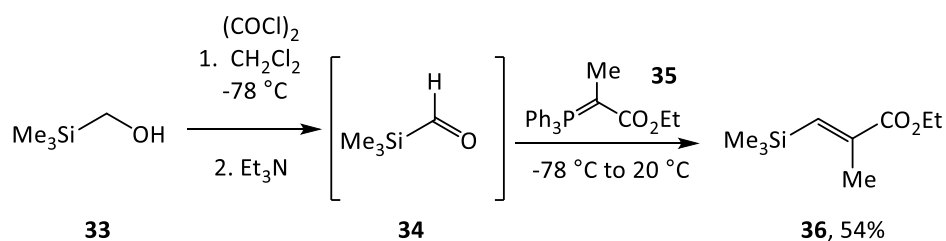
Scheme 9: The enantioselective synthesis of (+)-sterpurene **32**

2 TOP Reactions

The TOP strategy is a combination of an oxidation reaction with other synthetic transformations, termed by Taylor as a "Tandem Oxidation Process" (TOP). Such reactions can be very beneficial in terms of reducing the number of synthetic steps with maximization of complexity, being much less time consuming, and avoiding individual synthesis, isolation, and purification of the required intermediates. The conversion of alcohols into their corresponding oxidized forms is one of the fundamental transformations in organic synthesis as carbonyl derivatives can be transformed into many other functional groups.⁽¹⁷⁾

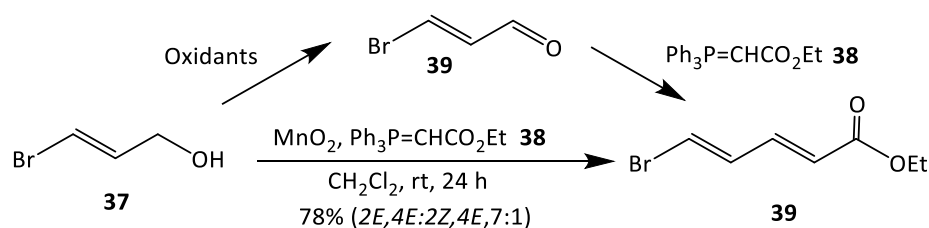
The origins of this work are in the first sequential oxidation-olefination process. Ireland and co-workers prepared ethyl 3-(trimethylsilyl) methacrylate **36** by successfully using a consecutive Swern oxidation-Wittig olefination

sequence, the unstable aldehyde was prepared and then treated *in situ* with stabilised phosphorane as a trapping reagent, which was added after the oxidation. This afforded a 54% yield of the desired product (Scheme 10). This process is however not ideal as the ylide cannot be added until the oxidation is complete because of incompatibility.⁽¹⁸⁾



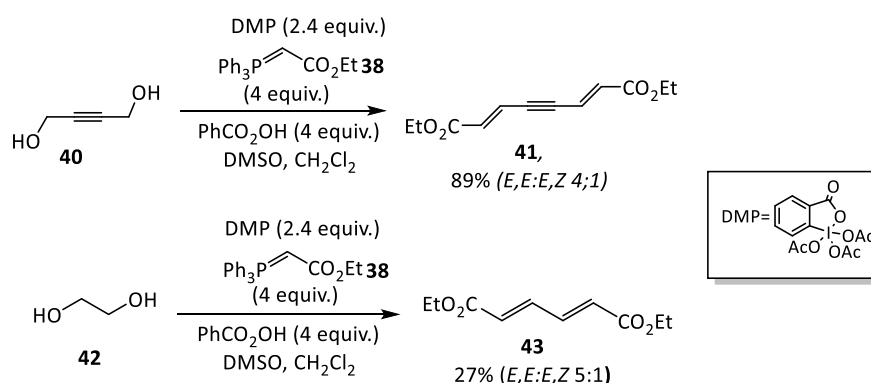
Scheme 10: Ireland's consecutive reaction synthesis of **36**

Substituted alcohols can also undergo tandem oxidation/Wittig olefination to afford α,β -unsaturated esters without the requirement for protecting group strategies. Taylor and co-workers reported a tandem oxidation reaction between (*E*)-3-bromo-propen-1-ol **37** and (carboethoxymethylene)triphenylphosphorane **38** in the presence of MnO_2 and CH_2Cl_2 , as shown in Scheme 11. Many examples of tandem oxidation process methodology have been reported by Taylor using a whole host of diverse conditions such as starting materials, solvents and temperature.⁽¹⁷⁾ These reactions work well for activated alcohols such as allylic, propargylic, α -hydroxyketones and benzylic alcohols and MnO_2 is readily available, stable and also easily removed by filtration from reaction.



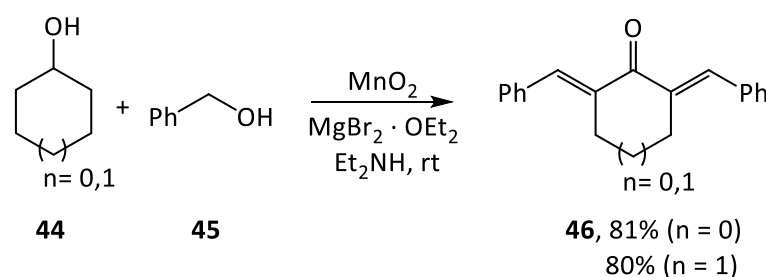
Scheme 11: A typical TOP reaction

Many oxidants including metal and non-metal based reagents and others can be applied in the oxidation reaction to give their oxidised form. Barrett employed Dess-Martin periodinane (DMP) in the oxidation of diols such as 2-butyne-1,2-diol **40** and 1,2-ethanediol **42** in the presence of (carboethoxymethylene)-triphenylphosphorane **38** to afford diester derivatives **41** and **43**. Although expensive, Dess-Martin periodinane is commercially available and widely utilized for the selective oxidation of alcohols to aldehydes containing sensitive functional groups. DMP is also good for alcohols that MnO_2 cannot oxidise such as those which are unactivated (Scheme **12**).⁽¹⁹⁾



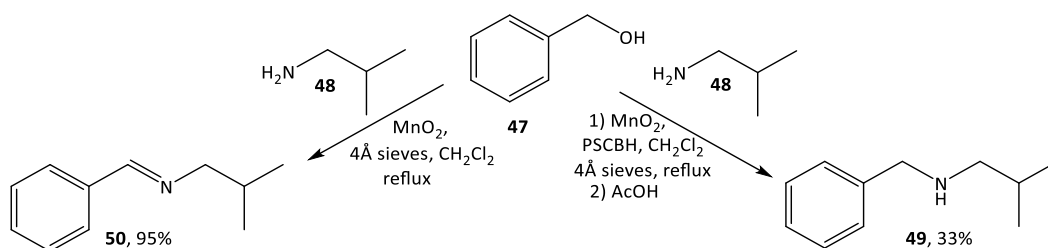
Scheme 12: Barrett's tandem oxidation-Wittig reaction with DMP as the oxidant

Recently, the wide scope of TOP processes has been demonstrated in the development of systems with variation of the reagents, oxidants as well as the conditions of reaction. For example, Mojtahedi and co-workers reported a protocol involving a novel one-pot synthesis of bisarylmethylidene **46** from cyclic alcohols. These reactions take place at room temperature to produce the corresponding compounds in high yields through aldol reaction-elimination of the *in situ* aldehyde to effect olefination (Scheme 13).⁽²⁰⁾



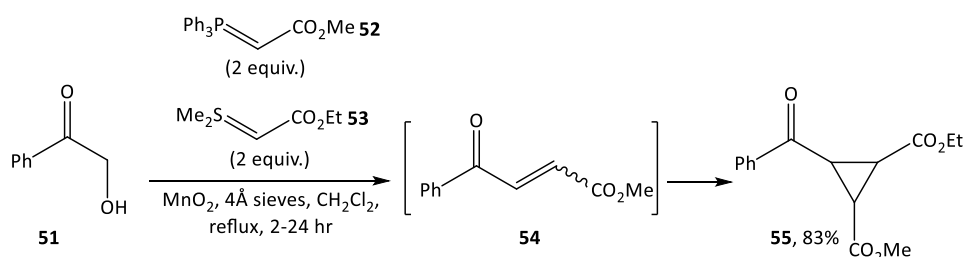
Scheme 13: TOP of cycloalcohols

New protocols are being increasingly used in tandem oxidation-anionic reactions utilizing other reactants such as amines instead of ylides. In 2001, a one-pot oxidation-imine formation-reduction sequence was developed for the conversion of activated alcohols into secondary and tertiary amines as well as imines (Scheme 14). Typically, the oxidation of alcohol **47** to the corresponding amine **49** and imine **50** yielded 33-95 %. This system proved to be more efficient by the combination of manganese dioxide as an *in situ* oxidant with polymer supported cyanoborohydride (PSCBH) as a compatible reductant for the preparation of amines.⁽²¹⁾



Scheme 14: The rapid synthesis of amines using TOP chemistry

An interesting TOP approach has been described by Taylor *et al* using the reaction of various alcohols with a combination of phosphorus- and sulfur-ylide at the same time in the presence of MnO_2 -mediated oxidant that includes three separated transformations in a single manipulation to synthesise polysubstituted cyclopropanes affording good yields, as depicted in Scheme 15.⁽²²⁾



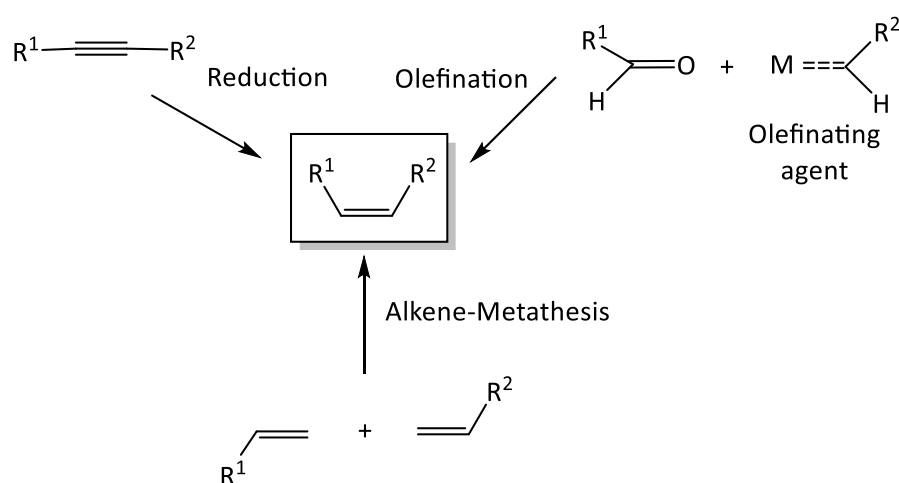
Scheme 15: TOP-cyclopropanes

Further to catalyst applications in organic synthesis, the presence of transition metals, such as caesium-mesoporous manganese oxide catalyst (meso Cs/MnO_x) have been reported as an efficient methodology for the construction of various esters from alcohols in one step under aerobic conditions by Suib and co-workers. They found the efficiency of the catalyst can be retained for the next usage without loss of its performance. The scope of this method provides a potential synthetic route to afford new compounds using TOP.⁽²³⁾ In

this context, the motive to research TOP reactions is comprehensible and more reasonable and it sounds inescapable that those reactions will play a considerable role in the future of the synthetic chemistry.

3 Olefination

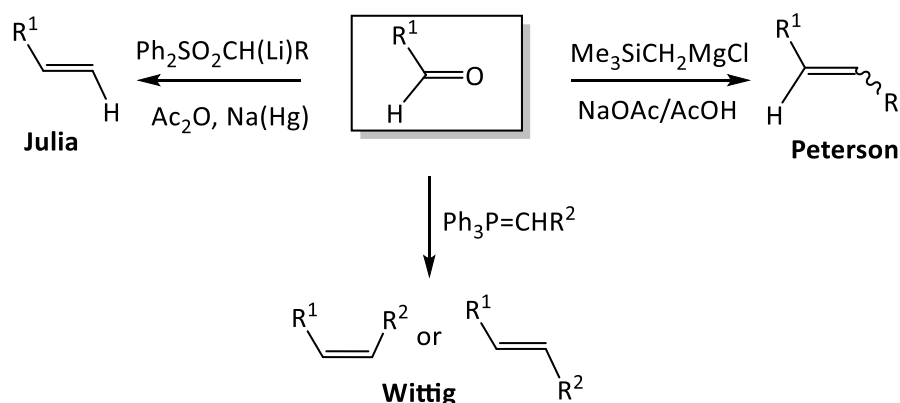
Alkenes are often important intermediates or synthetic targets and an impressive array of techniques have been assembled to prepare them. It is noteworthy that there are three predominate ways to synthesise alkenes, namely alkyne reduction, metathesis and olefination (Scheme 16). These methods are the reduction of alkyne by (Pd/H₂ or Na/NH₂), a reaction between two molecules of alkene in the presence of a catalyst, called alkene metathesis,⁽²⁴⁾ or the combination a carbonyl compound and a suitable olefinating agent together to generate alkene, which is known as olefination.



Scheme 16: Synthesis of alkenes

Generally, many processes for the construction of drugs and natural products *via* alkenes have been developed, including three widely used methodologies

for the trustworthy formation of olefins: the Wittig reaction,⁽²⁵⁾ the Peterson reaction,⁽²⁶⁾ and the Julia-Lythgo⁽²⁷⁾ / Julia Kocienski⁽²⁸⁾ olefinations. The olefination reactions in Scheme 17 illustrate the diverse olefination methods, each named after their discoverers.

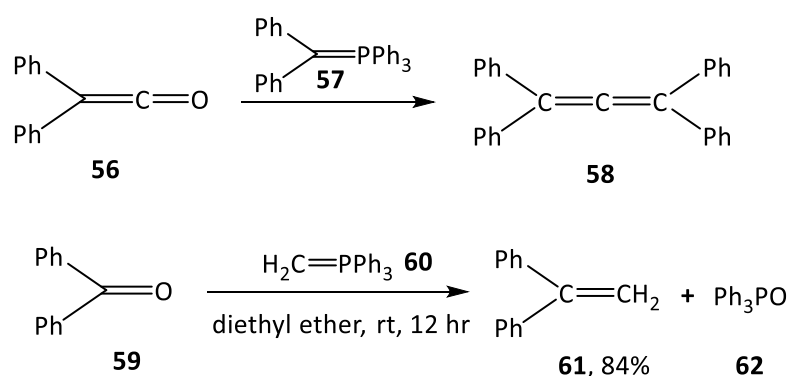


Scheme 17: Olefination reactions

3.1 The Wittig reaction

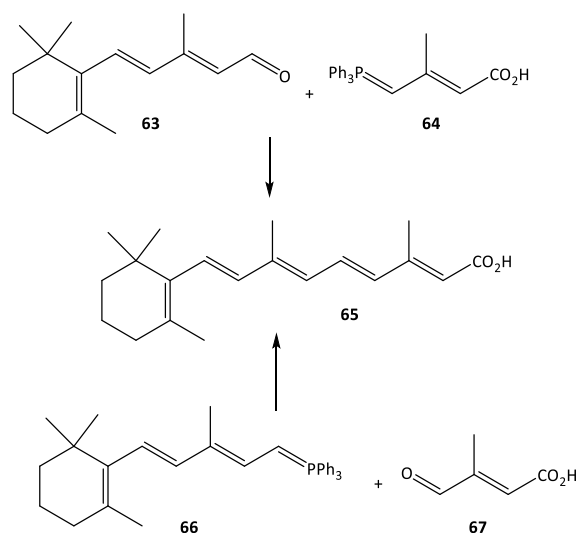
The Wittig reaction developed by Georg Wittig (1897-1987), remains one of the most effective reactions to form a C=C bond from a C=O bond and the ingenuity of this synthetic method is demonstrated by its extensive use in the chemistry of natural products.⁽²⁹⁾ Wittig olefination is the reaction between carbonyl compounds (aldehydes and ketones) and a phosphorane ylide known as the Wittig reagent. It is noteworthy that carbonyl components react with phosphorane ylide to afford olefins,^(30a) whereas sulfurane ylide give either olefins or epoxides depending on the stabilisation of ylides.⁽³¹⁾ The first record of a reaction between diphenyl ketene **56** and diphenyl ylide **57** was made by Staudinger in 1919, leading to the preparation of tetraphenylallene **58**, well before the work of Wittig.⁽³²⁾ In any case, this report stayed in isolation until in

1953 Wittig and Geissler⁽²⁹⁾ revealed that benzophenone and methylene ylide react to deliver 1,1-diphenylethene **61** and triphenylphosphine oxide in an 84% yield (Scheme **18**). Through the considerable endeavors of Wittig and his colleagues this technique was developed into to a general synthesis of alkenes from carbonyl compounds, and the reaction named after its developer.



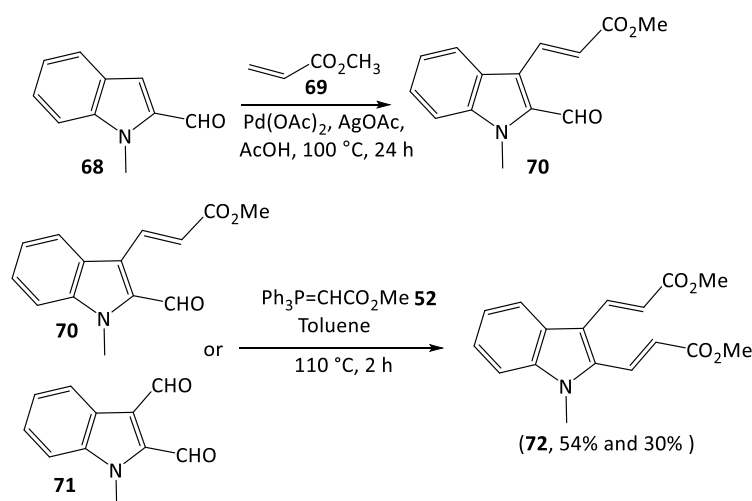
Scheme 18: Olefination reactions

Fortunately, and within a brief timeframe, the importance of this discovery was not ignored; researchers at the neighbouring BASF plant in Ludwigshafen utilised a new reaction of retinoic acid from the phosphoranylidene and the aldehyde (Scheme **19**).^(33a) Industry now produces natural and synthetic carotenoids and vitamins that are based on the Wittig reaction, such as the production of 600 tons annually of Vitamin A.



Scheme 19: Olefination reactions

In addition, Wittig reactions have been used in the preparation of the trienes core of indoles in the presence of palladium catalyst, by Pindur and Adam (1990).^(33b) It was noted that two different starting materials can be employed to synthesise *N*-methyl-2,3-divinyl-indole **72** using *N*-methyl-3-vinyl-indole-2-carbaldehyde **70** and *N*-methyl-indole-2,3-dicarbaldehyde **71**. Compound **70** was first prepared from the reaction of *N*-methyl-indole-2-carbaldehyde **68** in the presence of palladium acetate and acrylate **69** in toluene under thermal conditions. Both product **70** and product **71** can be used in the following step which is based on the Wittig reaction in toluene to afford the final product **72** in moderate yields of 54% and 30% respectively (Scheme 20).



Scheme 20: The synthesis of *N*-2,3-divinyllindole

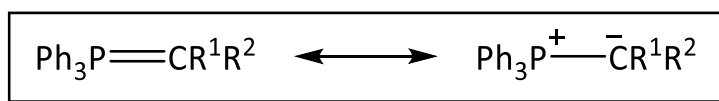
3.2 Phosphorane ylides

During the twentieth century, the development of phosphorous ylides⁽³²⁾ has been widely studied. Many researchers such as Bestmann, Corey, Schlosser, Trippett and others helped in the development of prominent improvements in phosphorane chemistry.⁽³⁴⁾ Phosphoranes have been classified into three classes depending on their delocalisation of the negative charge of carbon, which are: stabilised, semi-stabilised, and non-stabilised ylides.

One of the most common reagents in organic chemistry are phosphorane ylides; “a substance in which a carbanion is attached directly to a heteroatom carrying a high degree of positive charge”. For phosphorane ylides, the phosphorus atom formally carries a positive charge, and bonds with five groups in which carbon is the adjacent atom and has a negative charge.

The key factor in the reactivity of phosphorane is the presence of substituents (R^1 , R^2) at the ylidic carbon atom. However, these ylides can be categorised according to the substituents on the carbon atom, where electron releasing

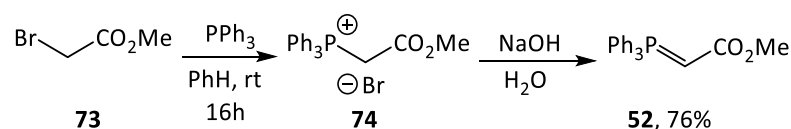
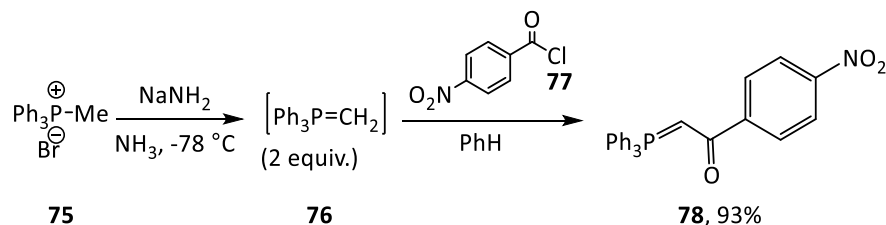
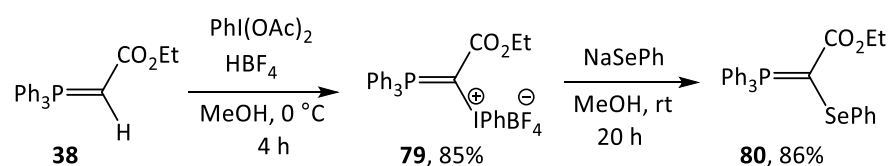
groups such as alkyl will increase their reactivity of the phosphorane. However, aromatic rings on the phosphorus atom will lessen their nucleophilicity to carbonyl compounds. In general, the unstabilised or semi-stabilised ylides are more active than stabilised ones. Keto-ylides are strongly enolised due to the localisation of negative charge on the oxygen atom rather than carbon atom of the ylide.



By far the most significant synthetic process for the preparation of phosphorane ylides is the salt method which is one of three major preparative routes:-

(1) - The "salt-method" (2) - Transylidation (3) - Umpolung "substitution"

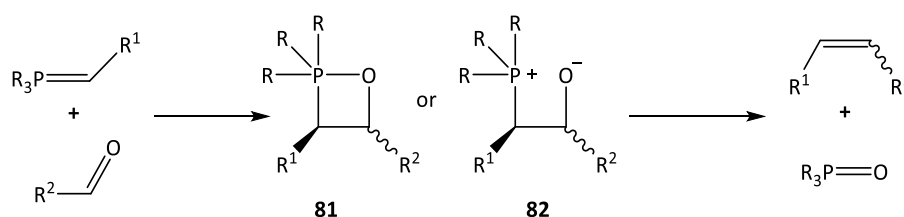
For example, the preparation of methyl (triphenylphosphoranylidene) acetate **52** is demonstrated in Scheme **21**. The same Scheme shows other methods in addition to the salt-method respectively.^(34a, 34b, 34c)

The "salt-method"TransylidationUmpolung substitution**Scheme 21:** The preparation of ylides**3.3 The mechanism of the Wittig reaction**

Many researchers have comprehensively studied the mechanism of the Wittig reaction. However, even today this mechanism is not completely understood and some its characteristics still prove contentious. In particular several reviews about the mechanism of the Wittig reaction have been reported by Schlosser,⁽³⁵⁾ Maryanoff,⁽³⁶⁾ and Kolodizhni.⁽³⁷⁾ However, the outcome of Wittig stereochemistry in most alkenes are generally accepted to proceed *via* one of two cases depending on the ylide used. Despite all the attempts to suggest a suitable mechanism, it has proved unfeasible to isolate, or even detect betaine intermediates spectroscopically. Basically, two-steps are involved in the Wittig reaction. The first stage comprises the nucleophilic addition of the carbon of the ylide to the (C=O) group, leading to the formation

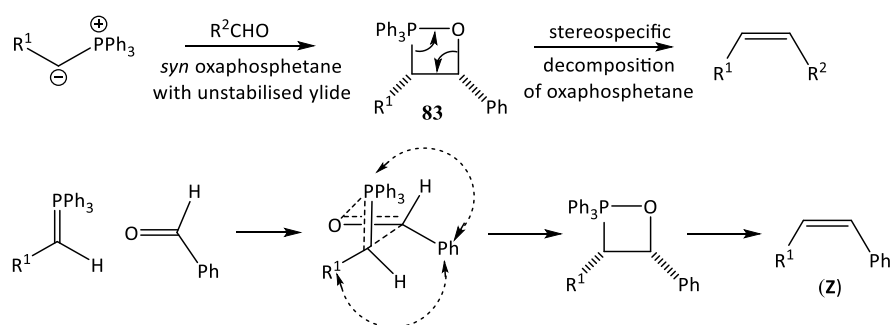
of a betaine. In this step, the presence of resonance stabilisation will reduce the nucleophilicity of the phosphorane between the carbanion and the groups on the carbon. Secondly, this intermediate is postulated to be converted to phosphine oxide and alkenes through a four-membered cyclic transition state.

The identification of the oxaphosphetanes structure **81** was made by Vedejs using NMR, confirming them as a key intermediates, and at that time was held to be pivotal to this mechanism (Scheme 22).⁽³⁸⁾ However, betaine **82** is the only the intermediate that has been identified either in the presence of lithium salts or chelating ligands on phosphorus in which to stabilise its charges.⁽³⁹⁾



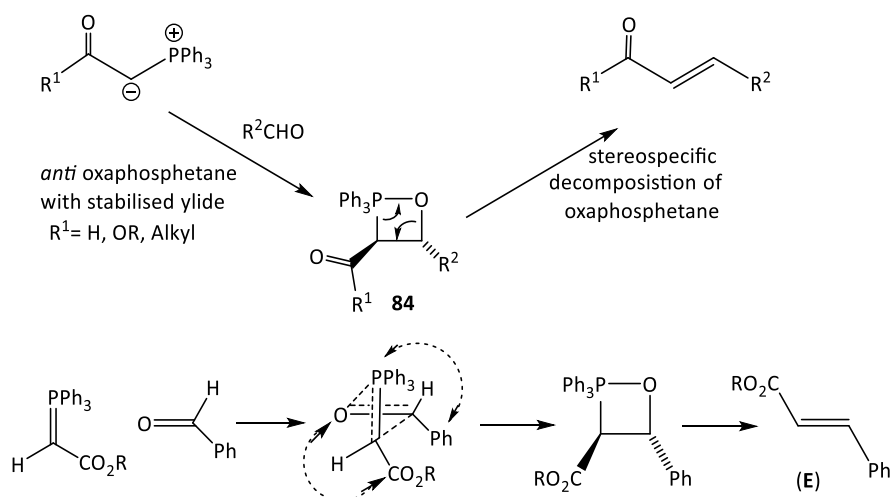
Scheme 22: Traditional Wittig mechanism

As can be seen, the Wittig reaction with unstabilised ylides is (*Z*)-selective which consists of a stereoselective first step by keeping the large substituents apart to form the *syn* oxaphosphetane, followed by an elimination step from this intermediate to afford a (*Z*)-alkene (Scheme 23).⁽⁴⁰⁾



Scheme 23: The stereochemistry of (Z) - alkene formation (*cis*)

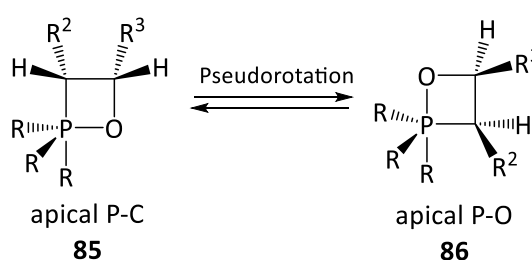
In contrast, the (*E*)-selectivity is favourable for stabilised ylides in the Wittig reaction, where the presence of electron withdrawing groups, such as an ester group, can stabilise the ylide carbanion *via* resonance delocalisation. The stereochemistry of the alkene product is settled by the stereochemistry of intermediate, which is shown in Scheme **24**. The addition occurs to minimise the dipoles by placing the EWG and the ylide opposite to each other.



Scheme 24: The stereochemistry of (*E*)-alkene formation (*trans*)

The process of construction of the oxaphosphetane intermediate **83** or **84** have been identified by many studies^(37, 41) *via* an asynchronous (2+2) cycloaddition. Despite intermediate **84** being more thermodynamically stable than

oxaphosphetane **83**, it still dominates for unstabilised ylides because of steric hindrance in the transition states (Scheme **23** and **24**). How products result from the decomposition of oxaphosphetanes is not obvious. There was an idea of this happening through a pseudorotation movement from P-C bond to P-O bond to explain the collapse, as shown in Scheme **25**. It was thought this collapse happens asynchronously where the breakage of the P-C bond is faster than formation of P=O bond.⁽⁴²⁾ Therefore, there is no decomposition if the process of pseudorotation is hindered or blocked.⁽⁴²⁾ Moreover, the study by Vedejs also found the rate of decomposition process is 108 times slower than the pseudorotation itself.⁽⁴³⁾



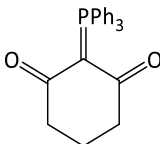
Scheme 25: Prospective pseudorotation in oxaphosphetanes

On the other hand, the use of stabilised ylides is mechanistically less well understood, where mechanistic studies have not given any proof of betaine or oxaphosphetane formation. The destabilisation of the oxaphosphetane leads to the collapse that could be due to the electron withdrawing groups on intermediate. Therefore, oxaphosphetane (*trans*) that resulted from the reaction of stabilised ylides produces a stable product under thermodynamic conditions.

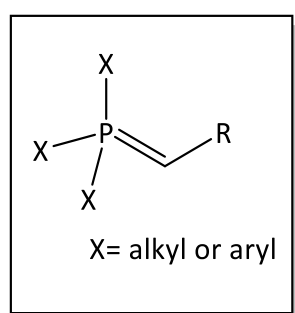
3.4 The reactivity of Wittig reaction

Both the ylide and carbonyl compound are important in Wittig reactivity. In general, aldehydes are more reactive than ketones and the type of reactivity can be compared with various ylide structures, as shown in the Table 1.

Table 1: Ylide reactivity (Y-reactive, N-non-reactive)

Class	Example	Aldehydes	Ketones
Unstabilised	$\text{Ph}_3\text{P}=\text{CHMe}$	YYY	YYY
Semi-stabilised	$\text{Ph}_3\text{P}=\text{CHPh}$	YY	Y
Stabilised	$\text{Ph}_3\text{P}=\text{CHCN}$	Y	N
Delocalised		N	N

Generally, the stereoselectivity of Wittig reaction depends on the structure of ylide that is easily predicted, which might be related to the mechanism. It is worthy to note that unstabilised ylides give (*Z*)-alkenes and stabilised ylides invariably produce (*E*)-alkenes as the principal isomers. Whereas, semi-stabilised ylides are mostly afforded unselective intermediates, resulting to mixtures of both (*E*) and (*Z*)-alkenes (Figure 1).



R = alkyl \longrightarrow non-stabilised ylides

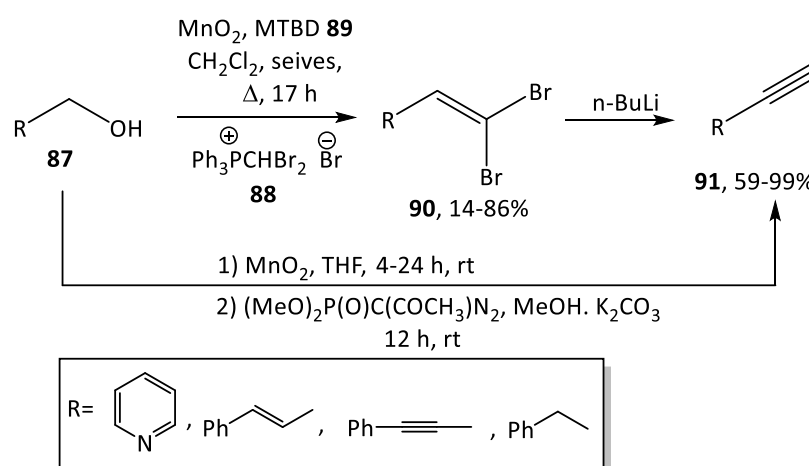
R = aryl, alkenyl \longrightarrow semi-stabilised ylides

R = carbonyl, ester, sulfone, ...etc. \longrightarrow stabilised ylides

Figure 1: Classification of phosphoranes

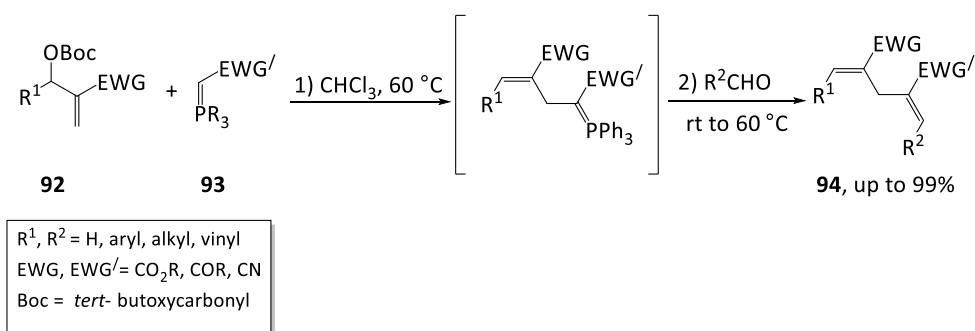
3.5 Tandem reactions involving Wittig reaction

TOPs are a significant tool in organic chemistry and Wittig reactions are widely used as a part of them to synthesise a wide range of products. For example, Taylor and co-workers have developed one-pot synthesis of 1,1-dibromoalkenes **90** from oxidation of a variety of activated alcohols such as benzylic, heterocyclic and propargylic alcohols in the presence of MnO_2 , phosphonium salts and MTBD (1-methyl-1,5,7-triazabicyclo[4,4,0]dec-5-ene) **89**, as well as the conversion of those resulting alkenes into their terminal alkynes in good to excellent yields, Scheme 26.⁽⁴⁴⁾



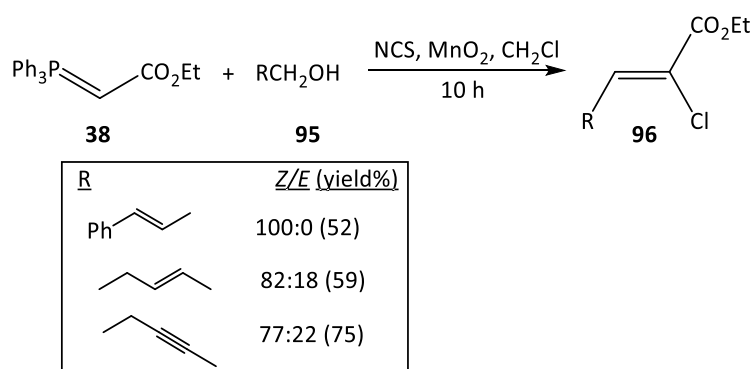
Scheme 26: Sequential one-pot MnO_2 oxidation/alkynylation synthesis

New developments are always being reported in Wittig Chemistry. For example, Xu and co-workers have recently prepared 1,4-dienes through the allylic alkylation of phosphorous ylides with allylic carbonates *via* a one-pot $\text{S}_{\text{N}}2'$ alkylation-Wittig strategy obtaining high to excellent yields, as shown in Scheme 27.⁽⁴⁵⁾



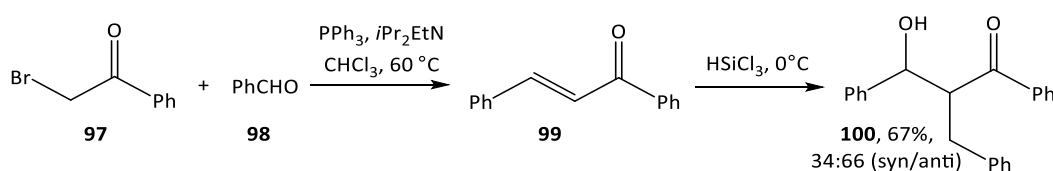
Scheme 27: One-pot $\text{S}_{\text{N}}2'$ alkylation-Wittig reaction

Recently, Sultan and co-workers (2017) raise several concerns about the handling of aldehydes and considered them to be unsuitable substrates. The authors investigated an efficient methodology to synthesise new one-pot chlorination/oxidation/Wittig olefination reaction for preparation of α -chloro- α,β -unsaturated esters from different alcohols. This method undergoes TOP reaction using *N*-chlorosuccinimide (NCS) as a chlorine source and manganese dioxide as the selective oxidant, affording moderate to good yields (Scheme 28).⁽⁴⁶⁾



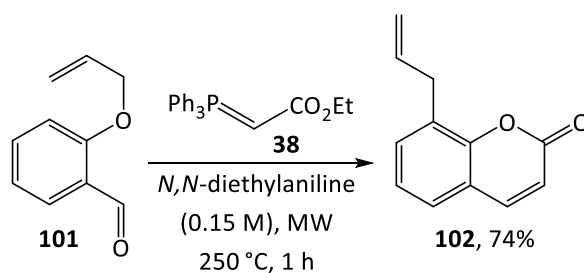
Scheme 28: TOP reaction of α -chloro- α,β -unsaturated esters using NCS and MnO_2

In recent years, there has been an increasing amount of literature on tandem Wittig reaction. In 2011, a one-pot Wittig/aldol reaction has been investigated by Toy and Lu, where this sequence is based on the synthesis of complex compounds. Scheme 29 illustrates the reaction of 2-bromoacetophenone **97** and benzaldehyde **98** (used twice) which are converted into the product **100** in 67% yield. Interestingly, it can be used with two different aldehydes in this reaction to afford new isomers. It was noticed that the anti-isomer is slightly preferable than the syn isomer in this reaction.⁽⁴⁷⁾



Scheme 29: Tandem one-pot Wittig/reductive aldol reactions

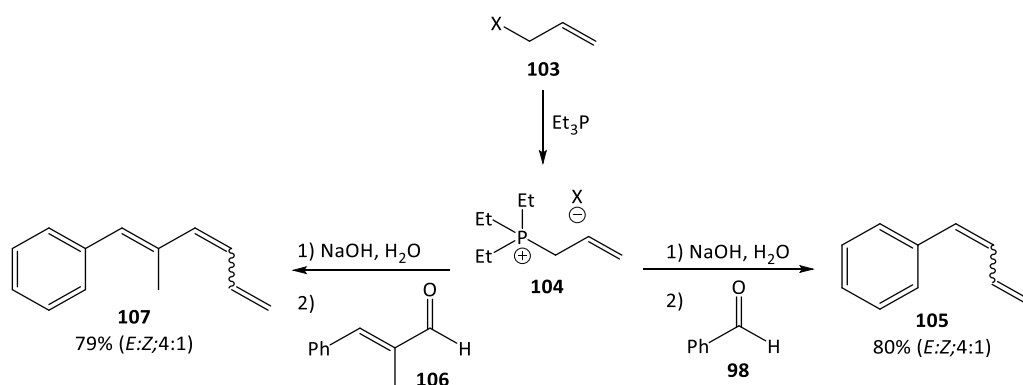
Additionally, the synthesis of substituted coumarins has been suggested by Schmidt and Riemer using a tandem sequence of olefination, Claisen rearrangement and cyclisation, under microwave conditions. Their analysis disclosed that the ability of synthesis of coumarin derivatives from various starting materials also affords reproducible yields using microwave irradiation at 250 °C in the presence of *N,N*-diethylaniline, as compared with the two steps separately. Gratifyingly, no isomers or variable compounds resulting from this sequence have been observed, as shown in Scheme 30. However, they noted that some other starting materials such as propargyl ether reacts under the same previous conditions but produce two different compounds, benzofuran and benzopyran.⁽⁴⁸⁾



Scheme 30: Tandem olefination/Claisen rearrangement/ isomerisation/ cyclisation sequence

3.6 Wittig reaction to synthesis trienes

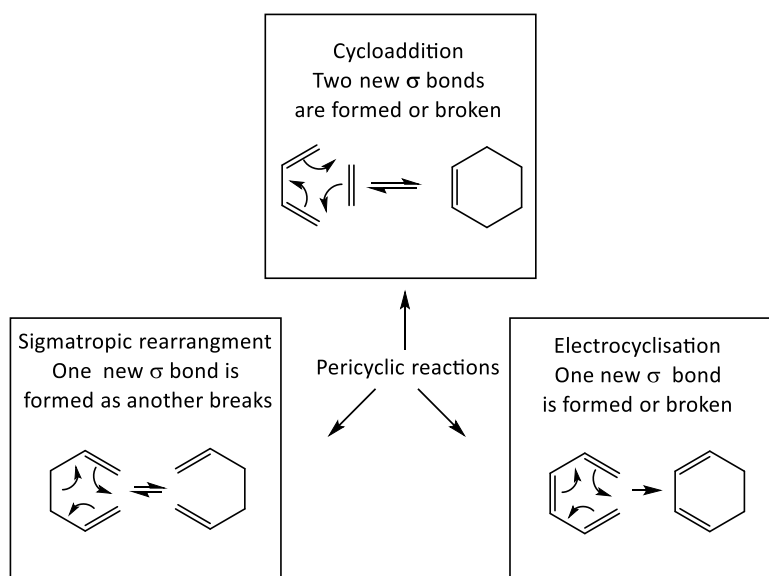
The synthesis of functionalised 1,3-dienes and polyenes by Wittig chemistry is somewhat rare. McNulty and co-workers have investigated the aqueous Wittig reaction of ylides derived from trialkylallyl phosphonium salts under basic conditions and those resulting semi-stabilised ylides were shown to react with aromatic, unsaturated, as well as enolisable aliphatic aldehydes to yield a diverse range of 1,3-dienes **105** and 1,3,5-trienes **107**. The isolated yields of the 1,3-dienes **105** compared to 1,3,5-trienes **107** were high in all cases investigated. The major advantage of this process is the easy separation of the water-soluble triethylphosphine oxide from the organic product which generally precipitated from the aqueous solution. The *E/Z*-selectivity is, however, modest because the ylides formed in the reaction are semi-stabilised, and therefore have intermediate selectivity (Scheme **31**).⁽⁴⁹⁾



Scheme 31: Synthesis 1,3-diene and polyene by the aqueous Wittig reaction

4 Pericyclic Reactions

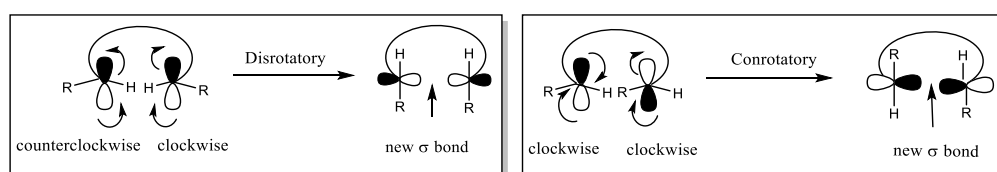
A pericyclic reaction is one that proceeds through a cyclic transition state. Pericyclic reactions are generally completely stereo-specific under thermal or photochemical conditions; that is; a single stereoisomer of the reactant forms a single stereoisomer of the product. Scheme 32 describes the types of pericyclic reactions which are distinguished by the number of σ bonds made or broken.⁽⁵⁰⁾



Scheme 32: Types of pericyclic reactions

4.1 Electrocyclisation reactions

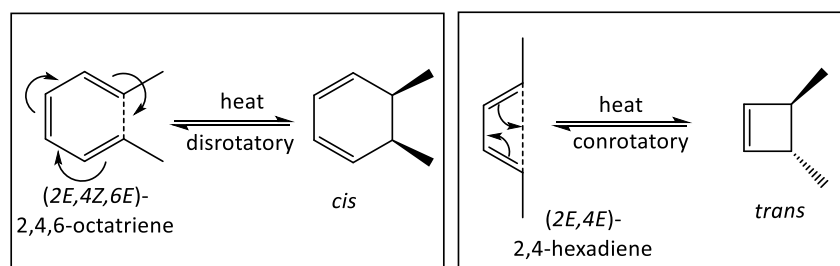
In an electrocyclisation closure, a conjugated polyene system is converted into a cyclic product in one step. The stereochemistry changes depending on whether irradiation (for example UV-light) or heat is used to promote the reaction. There are two possible modes for ring-closing and ring-opening of electrocyclisation reactions. The first mode is disrotatory where the σ bond is broken by twisting the termini in opposite directions. On the other hand, the other termini can be twisted in the same direction resulting in a conrotatory mode. The mode of the electrocyclisation reaction determines the stereochemistry of the product (Scheme 33).



Scheme 33: Two fashions of rotations

A set of rules based on orbitals and symmetry of pericyclic reactions was proposed by Woodward and Hoffmann in 1965,⁽⁵¹⁾ based on Frontier Molecular Orbital (FMO) analysis involving the HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Occupied Molecular Orbital). Electrocyclisation reactions can be done under thermal and photochemical conditions and the obtained products have different stereochemistries according to the method of promotion. Under thermal control, the electrocyclic ring closure of (*E,E*)-2,4-hexadiene, cyclisation happens in a conrotatory mode due to the HOMO of a conjugated diene having phases of the outermost lobes on opposite sides of

the molecule. As can be seen, one methyl group is pushed down and another one is pushed up, placing them in the *trans* relationship in the product. Conversely the thermal ring closure of (2*E*,4*Z*,6*E*)-2,4,6-octatriene occurs in a disrotatory mode that the HOMO of a conjugated triene has the same face of the molecule compared with the outermost orbital lobes, making a *cis* relationship in the product, as shown in Scheme 34.



Scheme 34: Thermal cyclisation of polyene

This is a specific example of the general process observed for conjugated polyenes with an *even* number of π bonds, which is shown in Figure 2. Both electrocyclic ring opening and closing reactions follow the same rules.

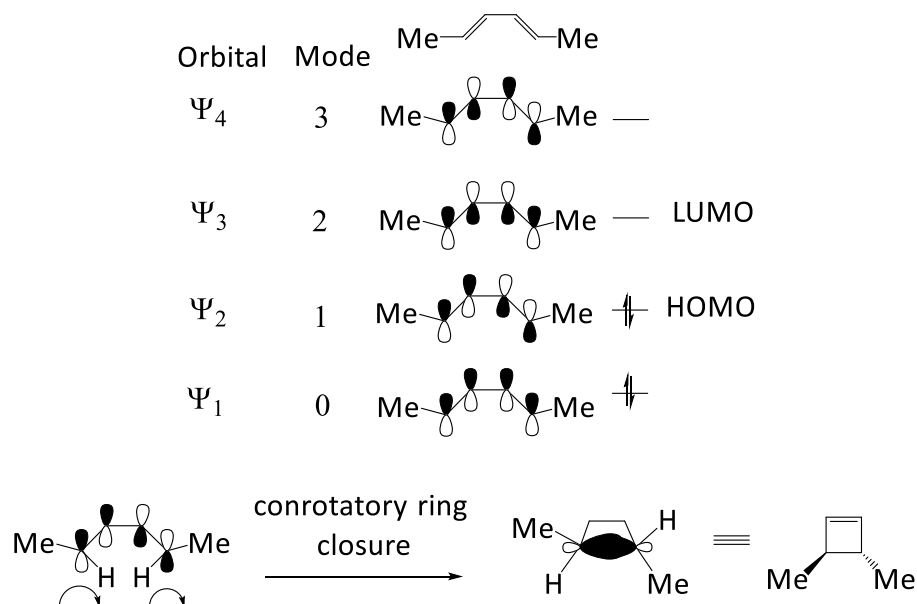
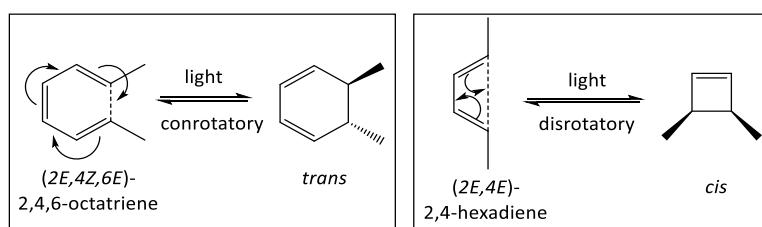


Figure 2: FMO for the π system of (2*E*,4*E*)-2,4-hexadiene

In terms of the photochemical cyclisation, the reactions follow similar rules as for the thermal electrocyclisations, but there is one important difference. As a result, the method of ring closure of a photochemical electrocyclisation reaction is reverse to that of a thermal one for the same number of π bonds. So photochemical electrocyclisation reactions occur in a disrotatory fashion for a diene with an *even* number of π bonds that means making a *cis* product. However, the same reactions for the conjugated triene occur in a disrotatory fashion by making a *trans*-product, as shown in Scheme 35.



Scheme 35: Photochemical cyclisation of conjugated systems

The photochemical irradiation of *cis*-3,4-dimethylcyclobut-1-ene is sufficient to promote an electron from the HOMO (Ψ_2) to (Ψ_3). This results in a singly occupied molecular orbital and generates a new excited state orbital HOMO*, as shown in Figure 3. Table 2 illustrates the summary of the Woodward-Hoffmann rules for electrocycatisation reaction of ring-closure and ring-opening.

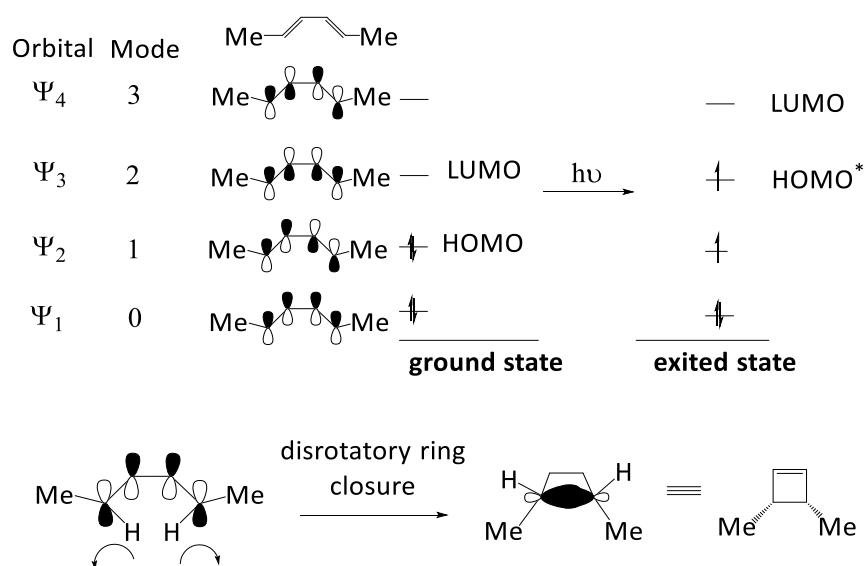


Figure 3: FMOs of (*E,E*)-2,4-hexadiene

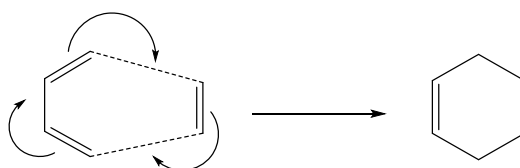
Table 2: The summary of WHR for electrocycatisation reactions

Number of π electrons	Thermal	Photochemical
$4n$	conrotatory	disrotatory
$4n+2$	disrotatory	conrotatory

4.2 Cycloaddition reactions

Two π systems are joined with the formation of two new σ bonds resulting in a cyclic product. The popular Diels–Alder reaction involves the addition of an alkene (dienophile) to a diene in one step where the stereochemistry of the product determined by the cycloaddition reaction based on thermal or

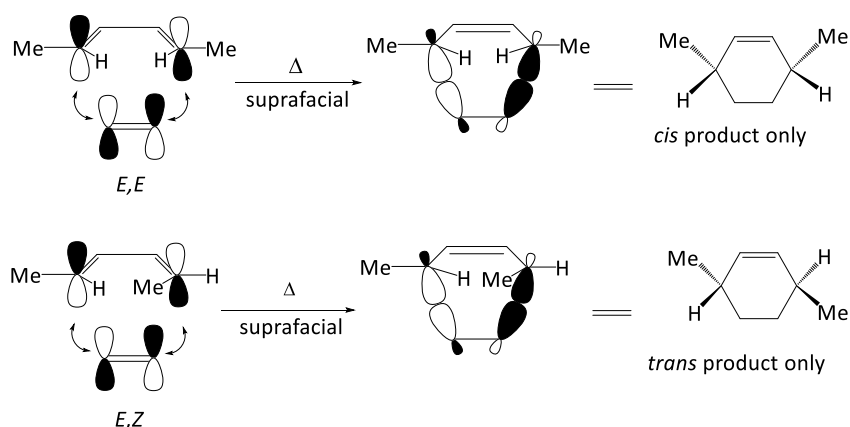
photochemical reaction conditions. Again the mode of cycloaddition is always opposite in thermal and photochemical reactions (Scheme 36).



The reaction is *usually* heat-promoted, but sometimes it is carried out photochemically.

Scheme 36: Cycloaddition reaction

[4+2] Cycloaddition reactions involve the movement of electron density from one reactant to another where the interactions occur from the HOMO of one component (the diene) to the LUMO of the second one (the dienophile). As a result, the (2*E*,4*E*)-2,4-hexadiene forms a cyclohexene with *cis* substituents whereas the (2*E*,4*Z*)-2,4-hexadiene affords a cyclohexene with *trans* substituents respectively, which shown in Scheme 37.



Scheme 37: The stereochemistry of Diels-Alder products

These observations of [4+2] cycloaddition reactions can be summarised in Table 3. In the suprafacial-suprafacial case, the cycloadditions are symmetry

and geometrically allowed but in suprafacial-antarafacial cases, the cycloadditions are symmetry allowed and geometrically forbidden.

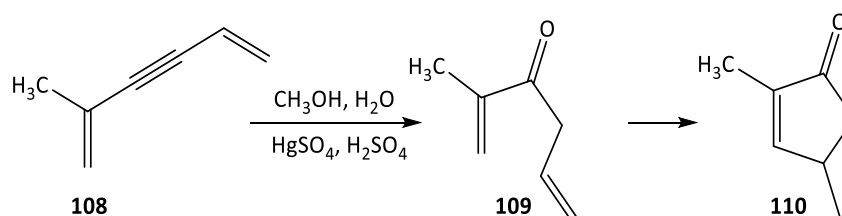
Table 3: The summary of WHR for cycloaddition reactions

Number of π electrons	Thermal cycloaddition	Photochemical cycloaddition
4n	suprafacial-suprafacial	suprafacial-antarafacial
4n+2	suprafacial-antarafacial	suprafacial-suprafacial

5 Nazarov Cyclisations

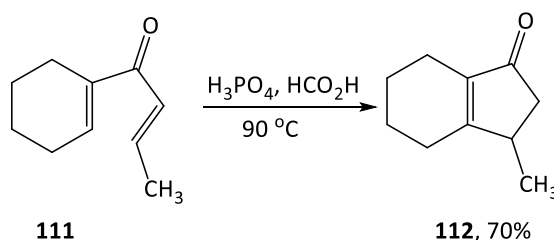
Nazarov cyclisation has been studied since the 1940s by Nazarov and Zaretskaya^(52a) and is a useful reaction for the synthesis of cyclopentenone compounds in the presence of Lewis acids such as FeBr₃, benzoic acid, ZrCl₄ and AlCl₃. A considerable amount of literature has been published on Nazarov cyclisation. These studies reported that the Nazarov reaction is a cationic electrocycloisatation, initially shown to be promoted by strong Lewis acid, but it was noticed later this reaction can be promoted even by mild Lewis acids.^(52b)

This reaction is carried out through a conrotatory 4 π -electrocyclic ring closure, as shown in Scheme 38, where Nazarov and co-workers found that the allyl vinyl ketones have been synthesised using the hydration of dienynes.^(52a)



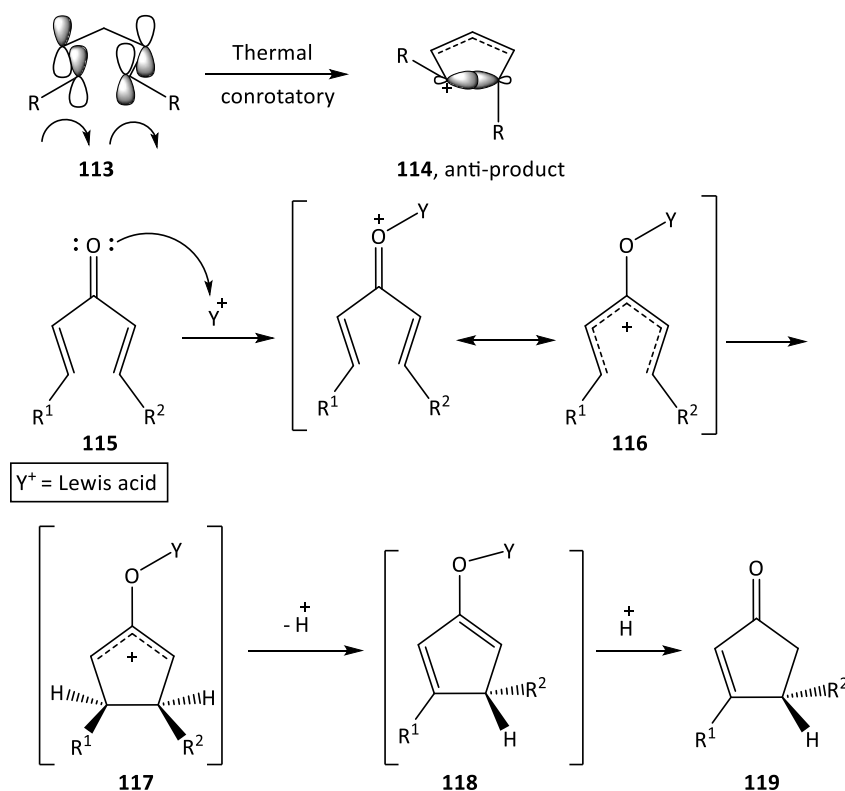
Scheme 38: Initial Nazarov cyclisation

The reaction of allyl vinyl ketone was formulated by Nazarov. Hence, Braude and Cloes^(53a) report another reactant for the synthesis of 2-cyclopentenone from α,α' -divinyl ketones (Scheme 39).



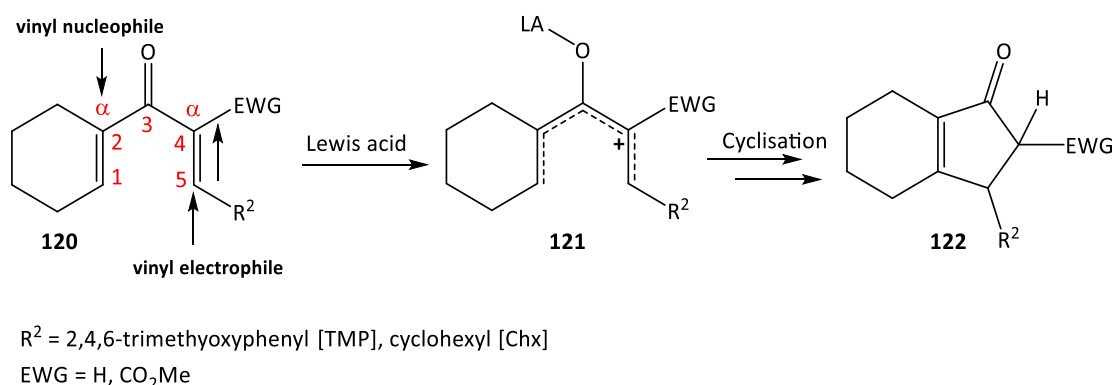
Scheme 39: Braude and Cloes' cyclisation

Mechanistic studies have demonstrated cationic intermediates in Nazarov cyclisation such as pentadienyl cation and an oxyallyl cation.^(53b) The key process is therefore a 4π -electrocyclisation to create a new carbon-carbon bond with two stereocentres. To illustrate FMO analysis of the Nazarov cyclisation, anti-product **114** is formed under the thermal conditions *via* the conrotatory ring closure of the ground state of HOMO cyclopentadienyl cation **113**, as shown in Scheme 40. Therefore, recent developments in the field of Nazarov cyclisation have led to a renewed interest in the activation of reaction by using Lewis acids. Scheme 40 illustrates the mechanism of Nazarov reaction where the substrate is activated by a Lewis acid generating a pentadienyl cation **116** that undergoes intramolecular 4π -electrocyclisation to form oxyallyl cation **117** as mentioned before. The re-protonation of enolate **118** gave cyclopentenone **119** as the final product. The above finding is consistent with the study by West.^(53c) West examined the impact of Lewis and Brønsted acids in Nazarov cyclisation.



Scheme 40: The FMO analysis and mechanism of Nazarov cyclisation

Another effect could influence on the activation of the Nazarov cyclisation, Frontier and co-workers⁽⁵⁴⁾ postulated that the presence of electron-withdrawing and electron-donating groups can polarise a pentadienyl cation as shown in Scheme 41. As can be seen, the electrocyclicalisation depends on the location of the stabilising substituent for example electron donating groups should accelerate the rate of reaction when in the α position (C-4) and decelerate in the β position (C-5).



Scheme 41: The effect of polarisation on Nazarov Reaction

The present study explores the influence of the electron withdrawing group (EWG) and R² on the dienone. Substrates with a carbomethoxy group, as an electron withdrawing group (EWG), at the α position (C-4) and (R² = 2,4,6-trimethoxyphenyl [TMP] and cyclohexyl [Chx]), can increase the reaction rates and be cyclised efficiently leading to improved regioselectivity of the double bond and to give excellent yields. On the other hand, it was noted that the cyclisation of substituent (EWG = H) was low-yielding (30-42%).⁽⁵⁴⁾

6 Diels-Alder reaction

The Diels-Alder reaction is the cycloaddition reaction of a conjugated diene to a dienophile to produce a cyclohexene. The reaction was discovered by German chemists Otto Diels and Kurt Alder, who received the Nobel prize for this achievement in 1950. The normal Diels-Alder reaction is favoured by electron withdrawing groups on the dienophile and by electron donating groups on the diene. In particular, the reaction is a stereospecific *syn* (suprafacial) addition with respect to both the alkene and the diene. There are two possible stereochemical orientations with respect to the diene. In the

endo mode the reference substituent on the dienophile is oriented toward the π orbitals of the diene. Whereas in the *exo* mode the substituent is oriented away from the π system, as illustrated in Figure 4.⁽⁵⁵⁾

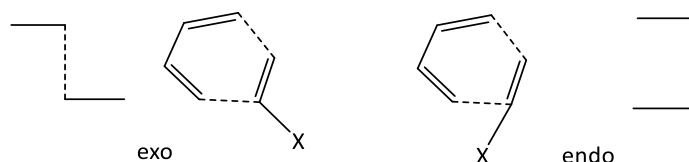


Figure 4: Two stereochemical orientations

The following scheme shows various substrates which are good and poor Diels–Alder components (Figure 5).

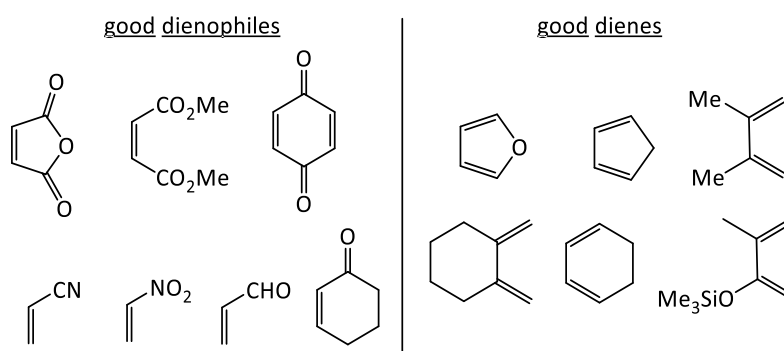
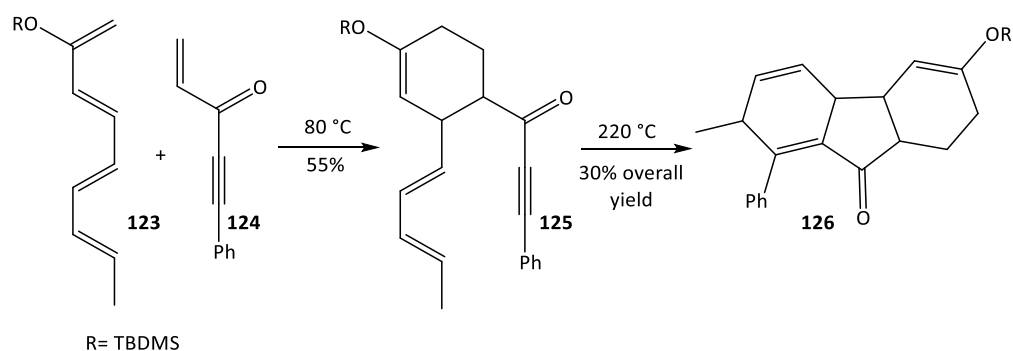
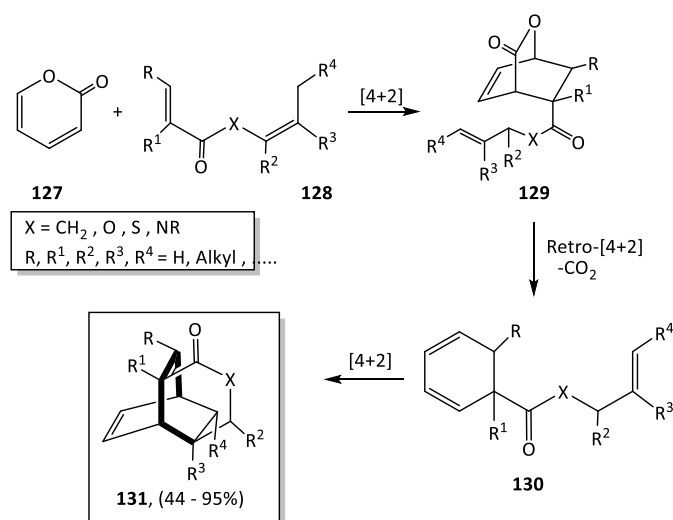


Figure 5: Diels–Alder components

Tandem cycloadditions utilise olefins to obtain new alkenes that can be reacted further. Cycloadditions are therefore well suited for use in tandem reactions,⁽⁵⁶⁾ and can even be used as all steps in a tandem process for example, Winkler has showed an alternative tandem Diels–Alder cycloaddition approach to the synthesis of fluorenone by the reaction of nona-1,3,6,8-tetraene and divinyl or alkynyl vinyl ketones which is based on Scheme 42.⁽⁵⁶⁾

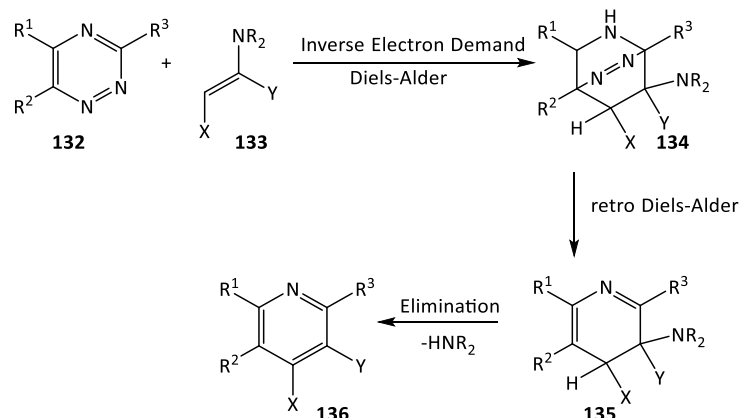
**Scheme 42:** Tandem /cycloaddition reaction

Cycloadditions can be also used in addition to other reaction types in a domino reaction. Marko has reported the synthesis of novel of tricyclic systems based on the reaction of 2-pyrone with α,ω -dienes. As can be seen, the final adducts without CO₂ were obtained as the sole product, as shown in Scheme 43.⁽⁵⁷⁾ Marko and co-workers examined various α,ω -dienes with the same starting material, which was 2-pyrone. Marko and co-workers have separated their bicyclic lactones, which can be considered as interesting intermediates in the synthetic chemistry *via* this methodology, which can be employed for the stereo-controlled preparation of highly oxygenated cyclohexane ring systems.⁽⁵⁸⁾



Scheme 43: Tandem process

The biological effectiveness of natural and synthetic substituted pyridine motifs is well known and it is therefore easy to understand the use of tandem reactions to make them.⁽⁵⁹⁾ There are two reports which have demonstrated the conversion of a range of substituted 1,2,4-triazines into highly substituted pyridines. Taylor and co-workers have developed a procedure called Tethered-Imine-Enamine (TIE) methodology. In the first report, they prepared the corresponding pyridines from the reaction of 1,2,4-triazines with cyclopentenone using chloroform, 4Å molecular sieves, and amines in order to afford substituted pyridines which are shown in Scheme 44 *via* Diels-Alder reaction.⁽⁵⁹⁾ Whilst in the second one, they extended their synthesis of pyridines by using some cycloketones and also reported a tandem oxidation process reaction as a direct methodology for the synthesis of substituted pyridines in good yields.⁽⁶⁰⁾



Scheme 44: TIE methodology

7 Indole alkaloids

One of the most significant nitrogen-containing secondary metabolites are indole alkaloids which include one or more indole/ indoline rings in their structures.⁽⁶¹⁾ It has been noticed that these structures have obvious pharmacological activities and clinical uses.⁽⁶²⁾ Most sources of indole alkaloids originate from plants, animals, prokaryotic microorganisms and eukaryotic organisms such as bacteria and fungi (Ascomycota).⁽⁶³⁾ The great interest by many academic scientists results from the high biological activity of these compounds. Macroline **137** and Sarpagine **138** indole alkaloids which are extracted from the plants to produce a drug popular in medicine.⁽⁶⁴⁻⁶⁶⁾ In addition, different indole alkaloids were extracted from *Alstonia* trees to give high biological activity against protozoal diseases.^(67, 68) Also Emetine **139**, one of the indole alkaloids, was compared with indolic natural products such as Tubulosine **140** to kill parasite species (Figure 6).

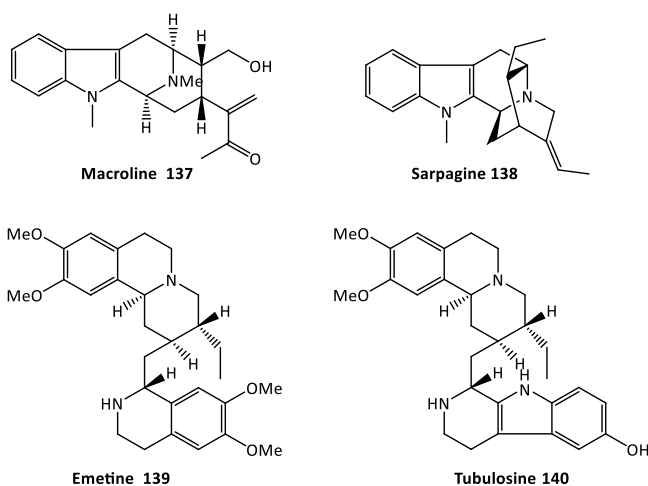


Figure 6: The Macroline, Sarpagine, Emetine, and Tubulosine indole alkaloids

7.1 Carbolines

Carboline derivatives (pyrido[2,3-*b*] indoles) are one of the biologically active compounds that are often used as antivirals and antitumor agents. As a result, the interest in the preparation of such compounds has been recently increased. These compounds form intercalation complexes with DNA molecules to inhibit the key DNA replication enzyme topoisomerase II.⁽⁶⁹⁾ Some publications have mentioned that carboline compounds were employed to reduce the anxiety, inflammation and stimulate the central nervous system.⁽⁷⁰⁾ Three types of carbolines can be classified depending on the location of nitrogen, hence, they are considered as the core structure of some natural products, as described in Figure 7.⁽⁷¹⁾

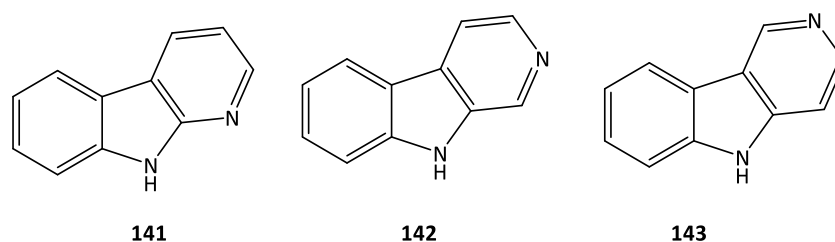
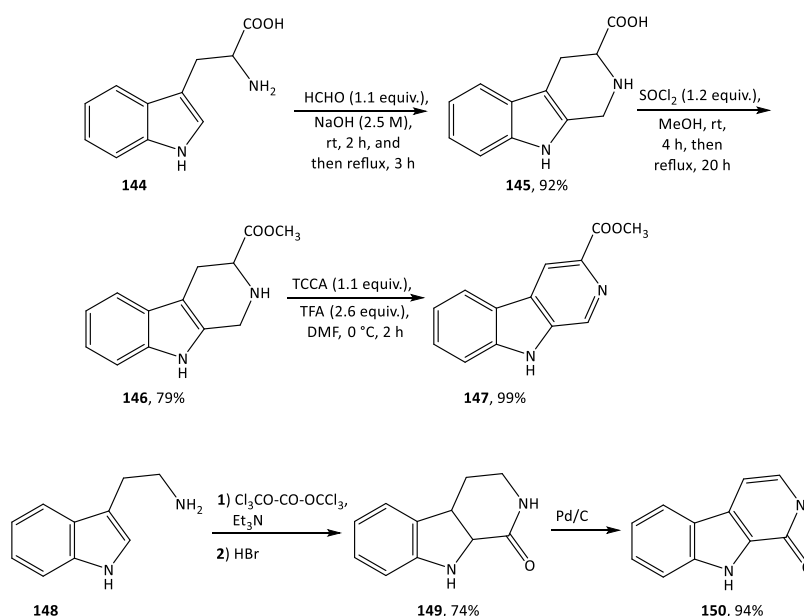


Figure 7: The simple structures of α- (141), β- (142), and γ-carbolines (143)

One of the most significant reactions that is employed for the synthesis of β-carbolines is Pictet-Spengler reaction. This system of synthesis can vary depending on the number of steps of reaction. An example of this is the study carried out by Konakahara and co-workers (2012)⁽⁷²⁾ in which they synthesised β-carboline derivatives through three steps by the Pictet-Spengler reaction of L-tryptophan⁽⁷³⁾ or of indolyethylamines⁽⁷⁴⁾ (Scheme 45).



Scheme 45: A conventional route to synthesis of β-carbolines derivatives

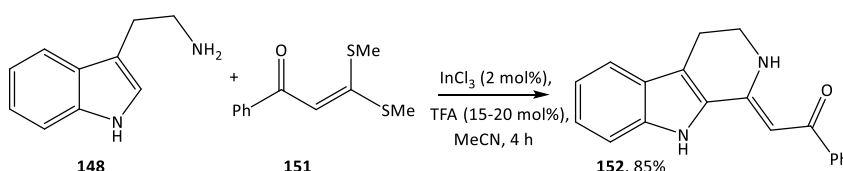
7.2 Synthesis of tetrahydro-β-Carbolines

Tetrahydro-β-carbolines (THβC) are one of the most widely used groups of indole alkaloids and have been extensively used for biological purposes. The

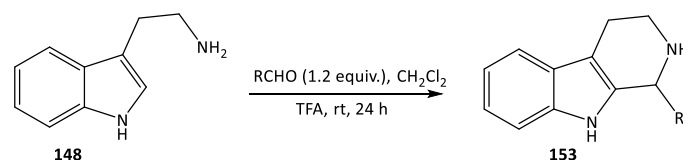
common structure of tetrahydro- β -carboline products consist of three linked-rings, with a partially hydrogenated pyridine ring. Tetrahydro- β -carboline derivatives play a vital role in the metabolism of animal and plant biological processes where the impact of these compounds on monoamine oxidases is shown by linking to benzodiazepine receptors.

There are excellent methodologies that are employed to synthesise TH β Cs such as the Pictet-Spengler reaction⁽⁷⁵⁾ and Bischler-Napieralski cyclisation,⁽⁷⁶⁾ however, other authors have formed TH β Cs in a variety of ways.⁽⁷⁷⁻⁸⁰⁾ For example, various TH β C compounds have been synthesised by Pictet-Spengler reaction and identified as inhibitors of the Breast Cancer Resistance Protein by Spindler and co-workers (2016).^(75d) According to a first definition suggested by Ross and co-workers (1998) who used ABCG2' term to refer to the gene which is the responsible for the breast cancer resistant protein (Scheme 46).^(75f)

Bischler-Napieralski cyclisation:



Pictet-Spengler cyclisation:

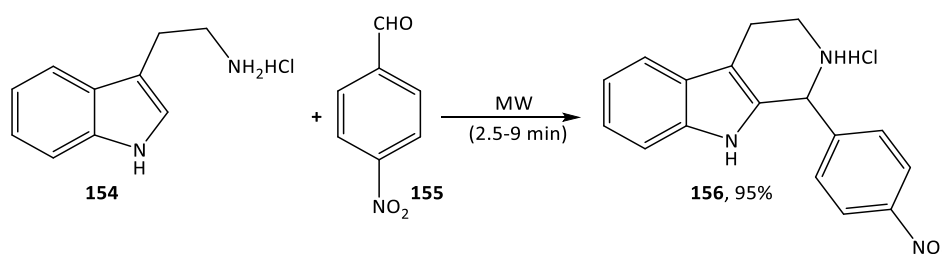


R = isobutyl (92%), phenyl (48%), 3-OCH₃-phenyl (72%), 4-CF₃-phenyl (97%)

Scheme 46: Pictet-Spengler and Bischler-Napieralski cyclisations of tryptophan to afford tetrahydro- β -carbolines

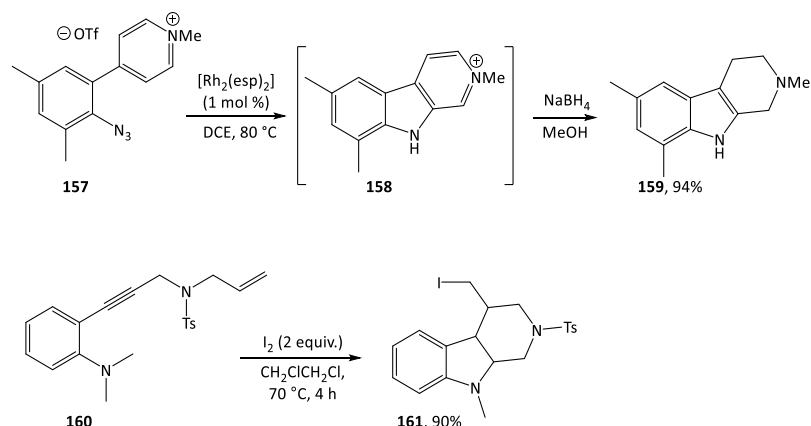
Recent developments in the field of the synthesis of TH β Cs have led to increasingly rapid advances in the field of employing new techniques in organic

synthesis. Microwave irradiation can play an important role in reducing reaction times and improving yields. Many studies have described the use of microwave in the Pictet–Spengler reaction for the preparation of TH β C scaffolds; however, most of this research used protic solvents with acid catalysed reactions.^(78a,81) Scheme 47 illustrates the Pictet–Spengler cyclisation of tryptamine hydrochlorides and a number of substituted aldehydes under solventless microwave irradiation for 2.5–9 min at 200 W affording compound such as **156** in good yields.



Scheme 47: The Pictet–Spengler cyclisation for the synthesis of tetrahydro- β -carboline hydrochloride

Furthermore, metal catalysed methodologies have been described for the construction of the TH β C scaffold. In 2012, Driver and co-workers used amination of 4-(2-azidophenyl) pyridinium derivatives using a rhodium catalyst to easily produce β -carbolinium ions from ortho-substituted aryl azides, followed by reducing the ions using NaBH₄ to give good recovery of tryptolines.^(77b) In addition iodine as a catalyst for tandem electrophilic cyclisation of 2-[3-(allylamino)prop-1-ynyl]anilines) derivatives was recently employed to prepare substituted 4-iodomethyl-tetrahydro- β -carbolines affording good to excellent yields (Scheme 48).⁽⁸²⁾



Scheme 48: The construction of the TH β C scaffold *via* metal-catalysed systems

7.3 Pharmaceutical importance of tetrahydro- β -carbolines (TH β Cs)

1, 2, 3, 4-Tetrahydro- β -carbolines are one of the most widely used groups of indole alkaloids and have been extensively used for their pharmacological importance that has been reported in 2005;⁽⁸³⁾ whereas, their biochemical functions have been studied in 2007.⁽⁸⁴⁾ In reviewing the literature, many reports can be found on their pharmacological properties and the relationship between TH β C compounds and its C1 stereocenters. All these reviews emphasized the role of their biological activities. Due to the high biological activity of C1-substituted TH β C substrates, many published papers significantly employed these compounds in pharmacological applications to be used as antiviral,⁽⁸⁵⁻⁸⁷⁾ PDE5-inhibitory,⁽⁸⁸⁾ antitumor⁽⁸⁹⁻⁹²⁾ and antimalarial⁽⁹³⁻⁹⁸⁾ drugs.

7.4 Antiprotozoal activity

There is evidence that TH β C compounds play a crucial role in exhibiting significant antiprotozoal activity, notably antimalarial, as shown in Figure 8. Globally, one of the major parasitic, infectious and life-threatening diseases in many regions of the world is malaria. The World Health Organisation (WHO)

found that more than one million people die and between 300 and 500 million are infected annually.⁽⁹⁹⁾ There would therefore seem to be a definite need for providing new antimalarial drugs *via* the isolation of antiprotozoal components from terrestrial plants and marine creatures. The relationship between the types of TH β C compounds and the treatment of malaria has been widely investigated by a number of studies.⁽⁹³⁻⁹⁸⁾

An example of this is the study carried out by Quinn *et al* (2010) in which the isolation of a natural product **162** from a Sponge, is called Ancorina sp, with the full elucidation of its structure and its antimalarial activity. It was noticed that the resulting compound show significant IC₅₀ values compared with each of chloroquine-sensitive (3D7) and chloroquine resistant (Dd2) strains of *Plasmodium falciparum*, namely 3.5 μ M and 5.4 μ M respectively.⁽⁹³⁾ The above similar finding is consistent with the study by Quinn. Chan *et al* revealed the same result of moderate antimalarial activity of similar compounds.⁽⁹⁴⁾

In 2012, the synthesis of a general structure of 1-substituted TH β C derivatives **163** was done according to the procedure of Gellis and co-workers with various substituents on the phenyl ring. They reported 20 substrates against the W2 culture of *Plasmodium falciparum* strains, which they have compared with pyrimethamine, chloroquine, proguanil and other compounds showing antiplasmodial activity. The results, as shown in this study, indicated that para-methoxy-substituted on phenyl ring at C1 stereocentre of TH β C compound possess the most active substrate where it gave IC₅₀ of 0.7 μ M (W2 IC₅₀ of chloroquine 0.7 μ M).⁽⁹⁵⁾ Despite the synthesis and creation of new generation of treatments to destroy malaria, there are still new colonies of malaria

displaying potent resistance against those drugs. The synthesised spiroindolone compounds have paid attention in the last years through assaying of its mechanism against *Plasmodium falciparum* and comparing them with that of the existing antimalarial drugs. From the data in this work, it is apparent that the effective compound NITD609 **164** provides the highest IC_{50} value of 0.2 nM.⁽⁹⁸⁾ Two years later, this antimalarial drug has been adopted into phase II clinical trials due to its high activity.⁽¹⁰⁰⁾

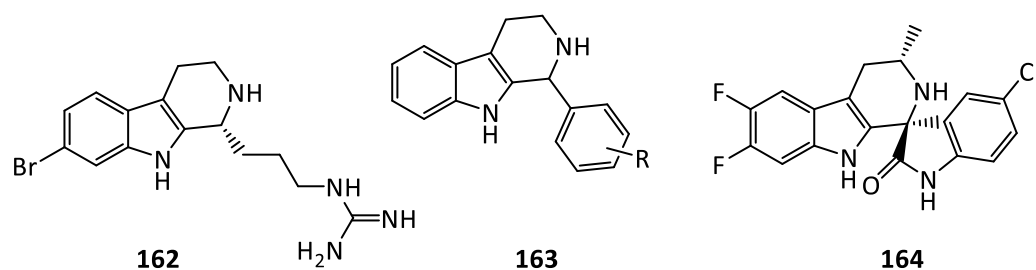
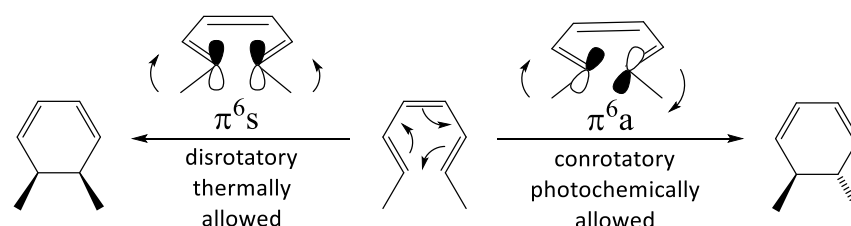


Figure 8: THβCs with antiprotozoal properties

Chapter 2 Results and Discussion I: Electrocyclisation

2 Introduction:

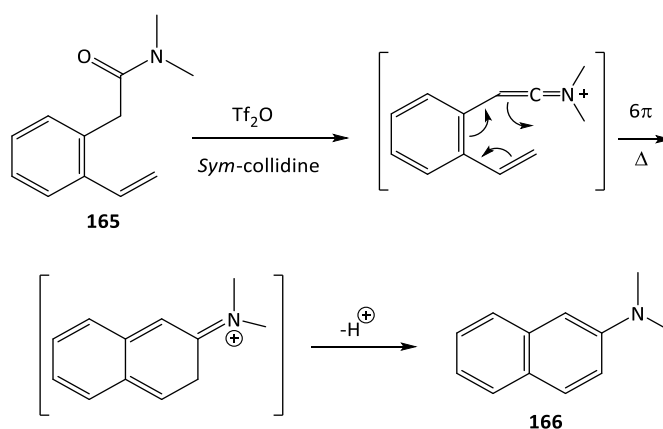
6 π -Electrocyclisation reactions are a relatively underused technique for the synthesis of complex motifs in organic chemistry which is surprising given the powerful nature of the reaction. These reactions are reversible therefore a conjugated polyene converts to a cycloalkene by ring closure, likewise, a cycloalkene can open to a conjugated polyene by ring opening. In this case, it was observed that the resulting stereochemistry of the final products in this reaction is depended on if it is carried out under photochemical or thermal conditions, as shown in Scheme 49.⁽¹⁰¹⁾



Scheme 49: Ring closure of a conjugated polyene thermally and photochemically

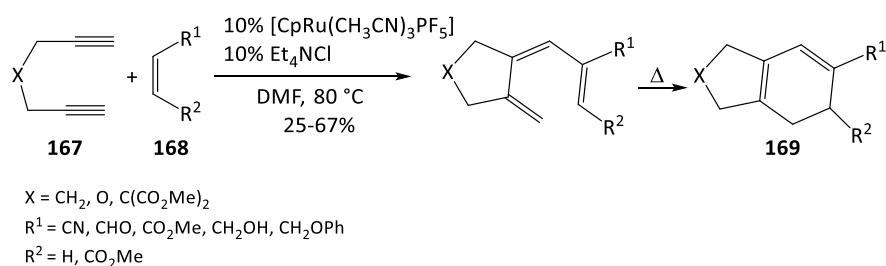
The conjugated π -system is often generated *in situ*, using various methods. In 2014, the use of vinyl ketene-iminium salts in 6 π /10 π -electrocyclisations was reported to form substituted naphthylamines by Mesmaeker *via* the reaction of *N,N*-dimethyl-2-(2-vinylphenyl) acetamide **165** with triflic anhydride in the presence of *Sym*-collidine (2,4,6-trimethylpyridine), which is shown in Scheme 50.⁽¹⁰²⁾ This reaction permitted a wide scope of functional groups from acyclic

to cyclic, electron rich and electron poor substituents and allowed access to more complex tricyclic compounds.



Scheme 50: Electrocyclisation of ketene-iminium salt to naphthylamine

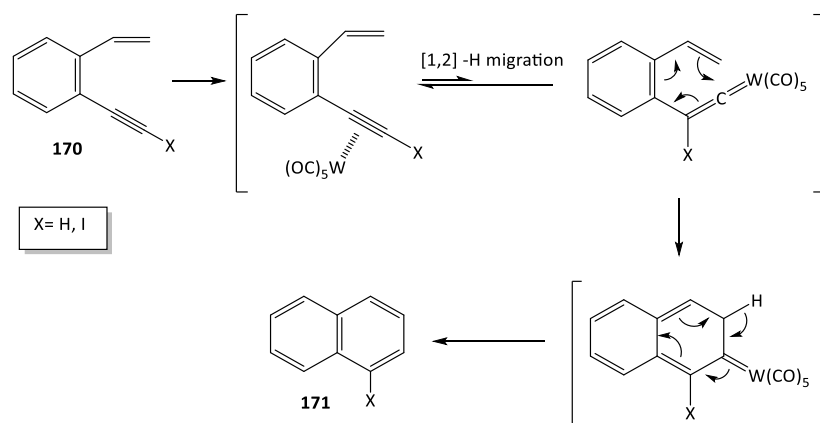
Electrocyclisation can also be achieved using transition metals as a catalyst to form the necessary triene to obtain the desired polycycles. For instance, Saa *et al* describe a new synthetic process including ruthenium catalysed addition of alkene to 1,6-diyne compounds followed by electrocyclic to afford bicyclic cyclohexadienes, as which shown in Scheme 51.⁽¹⁰³⁾



Scheme 51: The consecutive transformations of alkenes

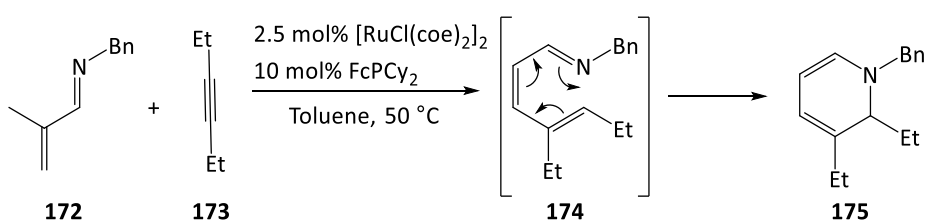
Furthermore, Liu has developed a novel tungsten mediated-electrocyclisation of *o*-[ethynyl] styrenes *via* tungsten vinylidene complexes to afford unusual 1,2-iodo and aryl shifts. In light of this, one of the best metal complexes for the electrocyclic of aromatic enynes, is $\text{W}(\text{CO})_5(\text{THF})$, which effected the

aromatisation of *o*-(iodoethynyl) styrene to give iodo-substituted naphthalene, which is based on Scheme 52.⁽¹⁰⁴⁾ A similar system has been reported by Akiyama.⁽¹⁰⁵⁾



Scheme 52: Aromatisation of substituted styrenes

As shown by Ellman and co-workers, a range of α,β -unsaturated imine substrates can be coupled with alkynes in the presence of a ruthenium catalyst to afford dihydropyridines through a 6π -electrocyclisation reaction. These reactions also work well for strained bicyclic enamines with bridgehead unsaturation, as shown in Scheme 53.⁽¹⁰⁶⁾

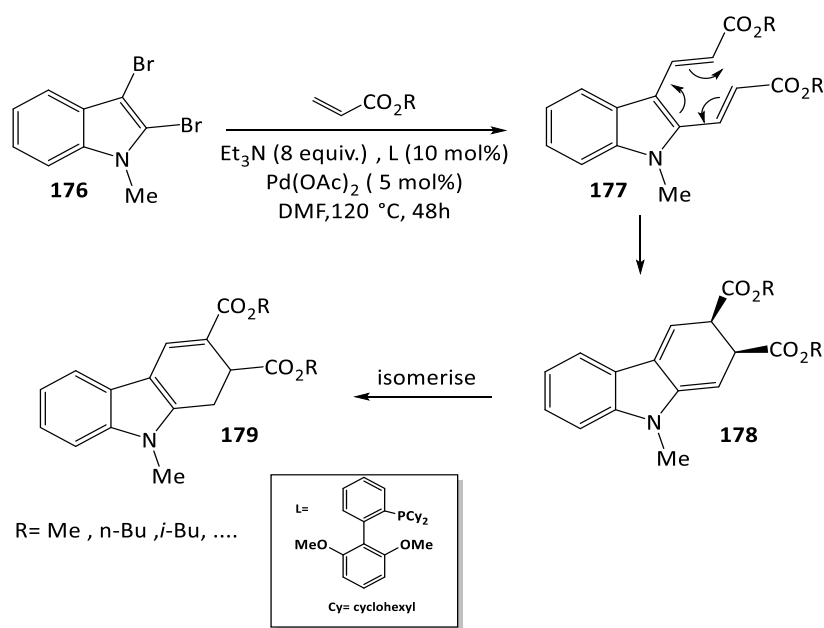


Scheme 53: Synthesis of dihydropyridines **175**

2.1 Carbocyclic electrocyclisation:

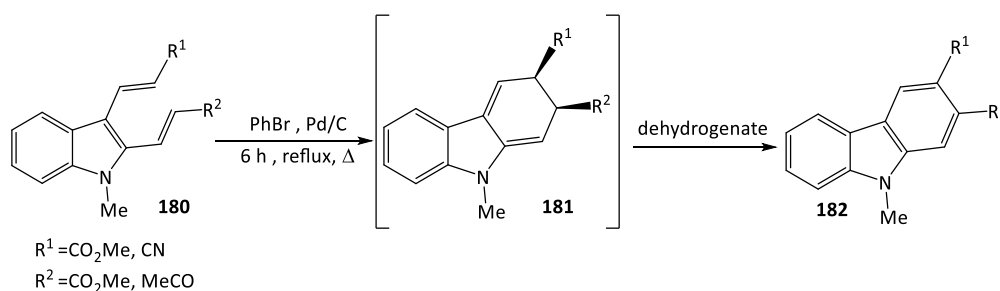
Several methods have been developed for the construction of new rings *via* electrocyclisation reactions. Langer has reported the formation of 1,2-dihydrocarbazoles by a domino twofold Heck- 6π -electrocyclisation from 2,3-dibromo-

N-methyl indole **176** and various acrylates catalysed by Pd(OAc)₂, which is presented in Scheme 54.⁽⁸⁾ Formation of the initial product breaks the aromaticity of the indole and therefore a rapid isomerisation takes place to generate the indole product and to restore it.



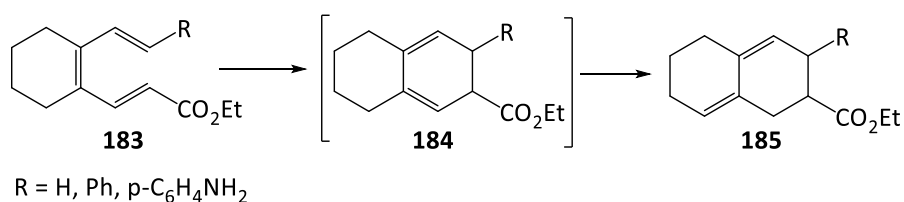
Scheme 54: Synthesis of 1,2-dihydrocarbazoles by 6 π -electrocyclisation

The successful synthesis of the carbazoles by electrocyclisation reaction methodology opened new possibilities for the preparation of many analogues of substituted carbazoles by utilising different conditions. Pindur has described the 6 π -thermal electrocyclisation of 2,3-divinyl-1H-indoles to annulated carbazole derivatives in yields of (7-84%). The reaction of **180** in boiling bromobenzene and in the presence of Pd/C as a dehydrogenation catalyst afforded **182** as novel compounds, as shown in Scheme 55.^(33b)



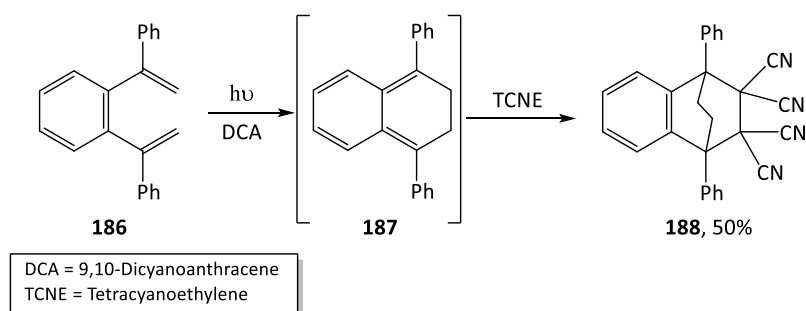
Scheme 55: 6 π -Thermal electrocyclicalisation by Pd/C

The three trienes, shown in Scheme 56, have been prepared and cyclised by Marvell and co-workers in the presence of inert solvents at 120-150 °C. This work also demonstrated the influence of the triene terminal substituents on the electrocyclicalisation process. The results indicated that the substituent interaction would play a dominant role in pericyclic reactions, and this effect is called a "push-pull" substitution. It has shown that the substituents in the *trans* positions have little steric interactions but such steric effects dominate in the *cis* position. Consequently, the push-pull substitution have little effect on rates of triene electrocyclicalisations.⁽¹⁰⁷⁾



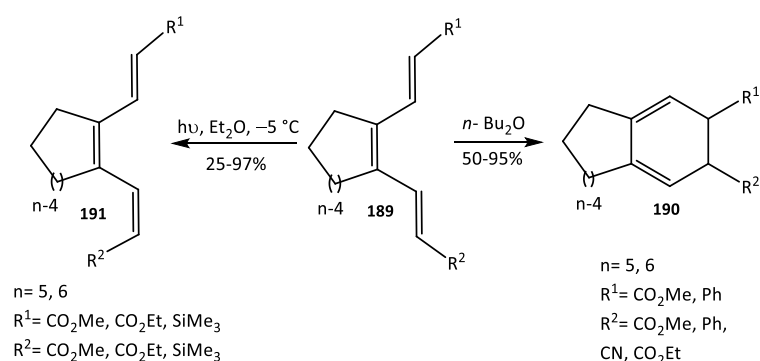
Scheme 56: Electrocyclicalisation for substituted trienes

6 π -Electrocyclicalisations can also proceed by photochemical promotion. For example, the electrocyclicalisation of 1,2-bis(1-phenylvinyl) benzene **186** to *o*-xylylene **188** demonstrated by Miyashi, is unique for the generation of *o*-xylylene derivatives; although the explanation of its mechanism has yet to be investigated (Scheme 57).⁽¹⁰⁸⁾



Scheme 57: Electrocyclisation of 1,2-bis(1-phenylvinyl) benzene **186**

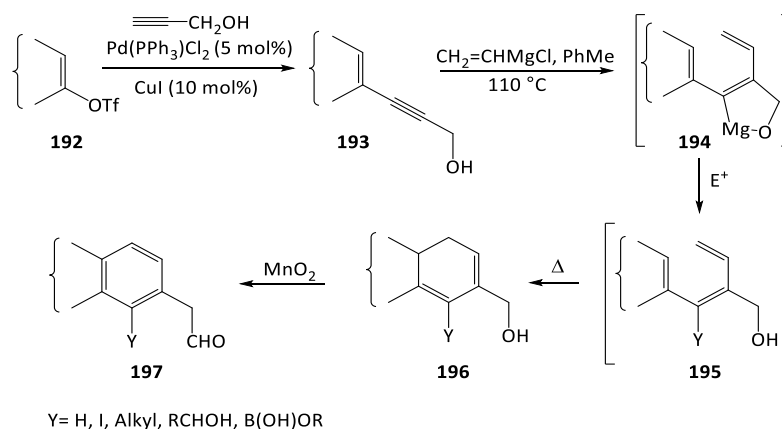
In view of the synthesis of the corresponding substituted cyclohexa-1,3-dienes by the above reaction, another method was devised, by de Meijere *via* heating in *n*-Bu₂O as a solvent. Scheme **58** shows the 6 π -electrocyclisation of the 1,3,5-(*E,Z,E*)-hexatrienes **189** to obtain compound **190**. Whereas, under the irradiation of **189** in diethyl ether at -5°C , no electrocyclisation reaction took place, instead the irradiation produced (*E* to *Z*) isomerisation (Compound **191**).⁽¹⁰⁹⁾



Scheme 58: Thermal & photochemical reactions of 1,3,5-(*E,Z,E*)-hexatrienes **189**

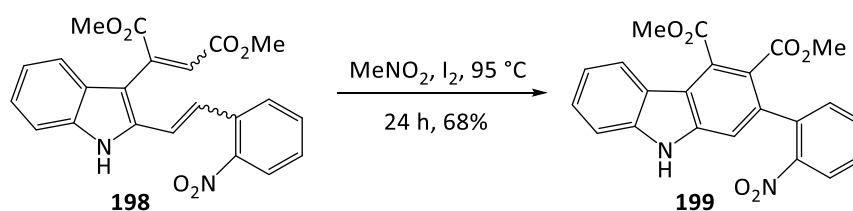
A new strategy for the aromatic annulation of cyclic ketones is the propargyl alcohol coupling reaction shown in Scheme **59**. In the presence of a palladium [0] complex as a catalyst, vinyl triflate **192** afford vinyl alcohol **193** that reacts with the vinyl Grignard reagent followed by 6 π -electrocyclisation *via* heating

the mixture to effect closure. Treatment with MnO_2 oxidised the diene formed into the arene product **197**.⁽¹¹⁰⁾



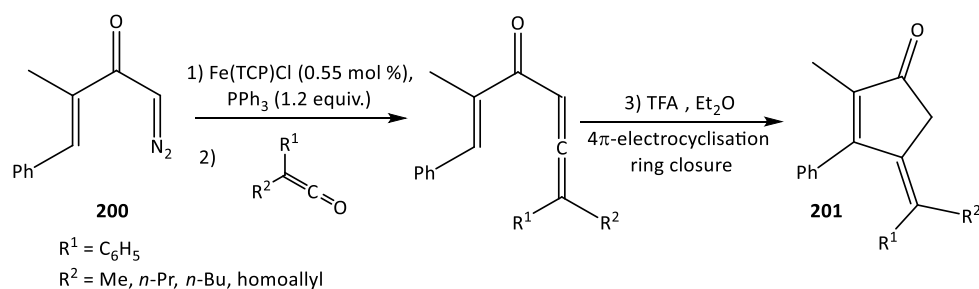
Scheme 59: Electrocyclic ring closure oxidation strategy

Tilve and co-workers have developed an efficient synthesis of indolecarbazole alkaloids *via* the thermal electrocycloisatation route of a 2,3-divinylindole **198** and subsequent oxidation to afford 2-nitrophenyl carbazole **199**. They examined several reaction conditions involving various solvents such as dichloromethane, DMSO and nitromethane (Scheme **60**).⁽¹¹¹⁾ Iodine was used in this case to oxidise the initial product to the carbazole.



Scheme 60: Electrocyclisation and aromatisation step of 2,3-divinylindole

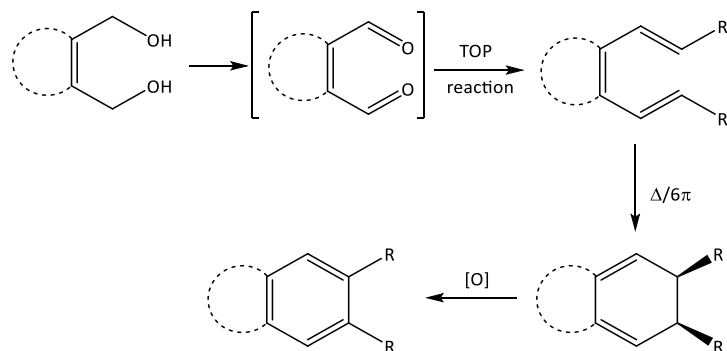
Tang has developed a novel synthesis of substituted cyclopentanones **201** *via* the transition metal catalysed reaction of diazo compounds with ketenes, as shown in Scheme **61**.⁽¹¹²⁾ The initial alkene undergoes acid catalysed Nazarov 4π -electrocyclisation ring closure to give the final product.



Scheme 61: One-Pot synthesis of some substituted cyclopentanones

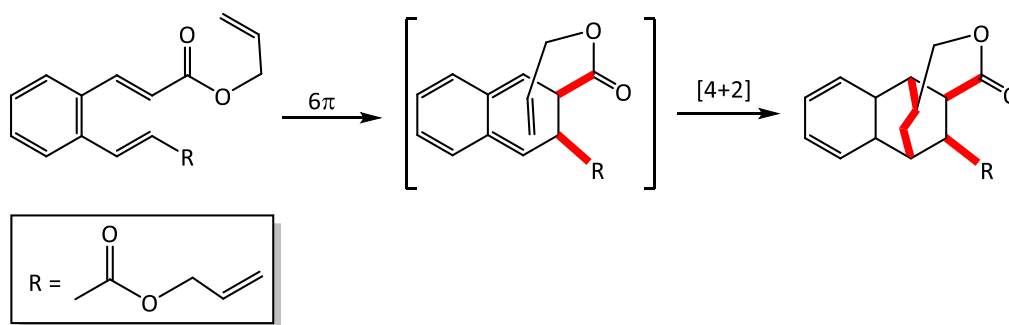
2.2 Project Introduction

The objective of this project was to extend the concept of TOP chemistry to enable the elaboration of simple to complex molecules (trienes) through the reaction of dieneols with phosphorane ylides in the presence of oxidants. A proposed four step oxidation-Wittig, 6 π -electrocyclisation, and oxidation sequence would construct the C-C bond and examine 6 π -thermal ring closure/oxidation to make rings (Scheme 62).



Scheme 62: The proposed sequence of this project

The study and development of this process would unlock a general method for the construction of C-C bonds from diols under mild reaction conditions *via* TOP reactions, followed by examination of tandem 6 π -thermal electrocyclisation/Diels-Alder reactions of synthesised trienes. Scheme 63 illustrates an attempted route to synthesis complex compounds.



Scheme 63: An attempted application of trienes *via* tandem 6π -thermal electrocyclisation/Diels-Alder reactions

2.3 Preparation of substrates:

To test this methodology the synthesis of following dieneols was undertaken individually, as shown in Figure 9:

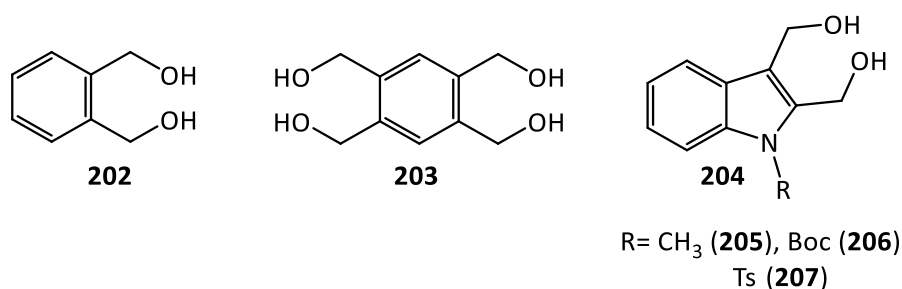
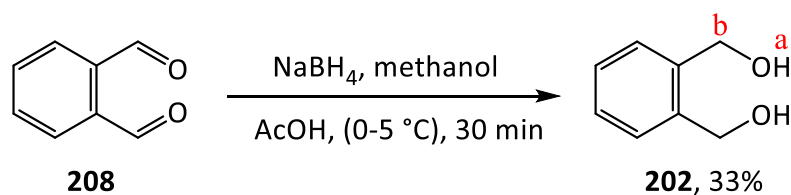


Figure 9: The starting materials (synthesised diols)

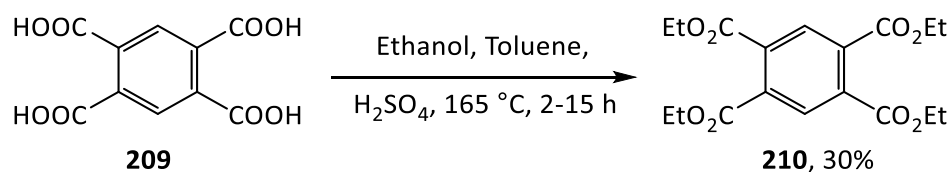
The initial substrate chosen was benzene-1,2-dimethanol **202**. Although part of the conjugated 6π -system is embedded into the aromatic benzene ring, the ease of preparing this substrate made it good starting point. The reduction of phthalaldialdehyde **208** to afford benzene-1,2-dimethanol **202** by using sodium borohydride in methanol, was accomplished in 33% yield, as shown in Scheme 64. The low yield reflects the difficulty in isolating the polar product.



Scheme 64: Reduction of aldehyde **205** to alcohol **202**

It was shown from the analysis of $^1\text{H-NMR}$ that the protons of aldehyde group disappeared and were replaced by the hydroxyl group (**a**, 3.07 ppm), and the methylene group (**b**) was appeared at 4.76 ppm. Further analysis noted that no $^{13}\text{C-NMR}$ peak of aldehyde was observed; while at peak 64.05 ppm was attributed to ($-\underline{\text{C}}\text{H}_2-$) groups.⁽¹¹³⁾

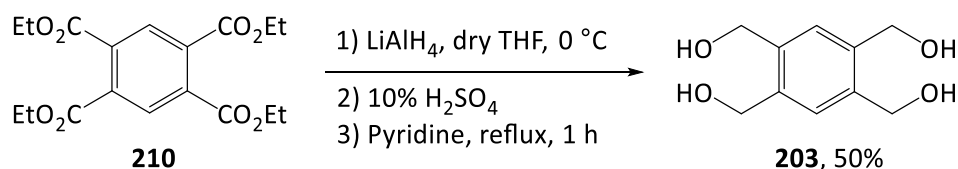
Additionally, The transformation of pyromellitic acid **209** to tetraethylpyromellitate **210** was accomplished in 30% yield according to the Bailey and co-workers procedure.⁽¹¹⁴⁾ Despite the use of azeotropic esterification, the reaction does not work well, as shown in Scheme 65.



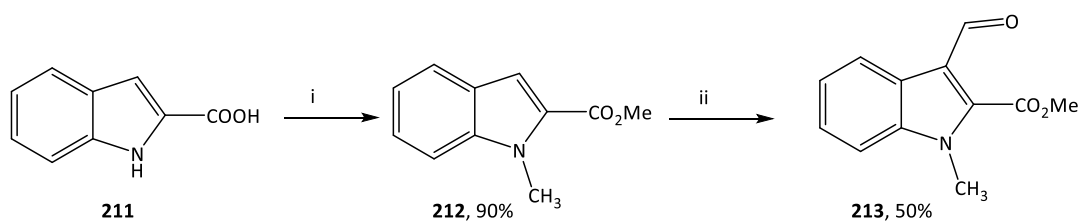
Scheme 65: Fischer esterification of pyromellitic acid **209**

Tetraethyl pyromellitate **210** reduces to 1,2,4,5-tetrakis(hydroxymethyl) benzene **203** *via* reduction reaction using Lithium aluminum hydride in anhydrous THF (Scheme 66). The main disadvantage of this experimental method is that no **203** was obtained after its workup. Therefore, this compound was prepared by adapting the procedure used by Lenz (1989)⁽¹¹⁵⁾ in which the crude product of the previous reduction reaction was acidified by H_2SO_4 and then refluxed in pyridine for an hour affording a white solid as a

product. This experiment yielded 50% of **203**. NMR analysis confirmed the formation of the desired product; ^1H -NMR peaks were found at 4.50 ppm (s, 8H) and 7.40 ppm (s, 2H) belonging to ($-\underline{\text{CH}_2}\text{-OH}$) and the protons of the benzene ring respectively.

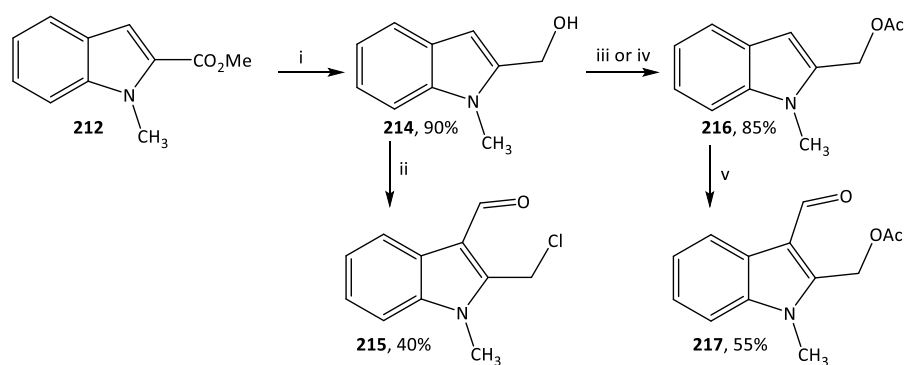


Scheme 66: The reduction reaction of tetraethyl pyromellitate **207** by LiAlH_4 Methyl-*N*-methyl-2-indole-carboxylate **212** was successfully prepared by esterification of 1H-indole-2-carboxylic acid **211** in the presence of methyl iodide in DMF under different basic conditions. Its ^1H -NMR spectra further confirmed these structures. Thus, the peak at 4.12 ppm (s) was assigned to the ($\text{N}-\underline{\text{CH}_3}$) of **212**, while ester groups ($\text{O}-\underline{\text{CH}_3}$) appeared at 3.95 ppm (s).⁽¹¹⁶⁾ The second of the process, based upon Bennasar's methodology, was the Vilsmeier formylation reaction (Scheme 67).⁽¹¹⁷⁾ The reaction was performed at 50°C , the crude was neutralised with a solution of 2M sodium hydroxide (NaOH) as a base to afford the final product methyl 3-formyl-1-methyl-2-indole carboxylate **213** in 50% yield. NMR analysis showed a singlet peaks at 10.62 ppm (CHO) and the proton at the position 3 on the pyrrole ring (7.33 ppm) disappeared and was replaced by the aldehyde proton, indicating this reaction proceeded as planned.⁽¹¹⁸⁾



Scheme 67: The synthesis of aldehyde **213**: (i) CH_3I , K_2CO_3 , DMF, 80°C , 3-4 days; ii) POCl_3 , DMF, rt (30 min), then heating at 60°C , 3 h.

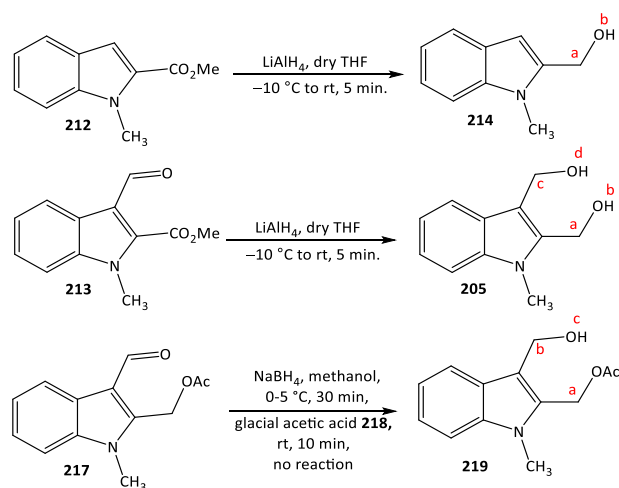
Compound **212** was converted into the corresponding 2-hydroxymethyl-1-methyl indole **214** *via* a reduction reaction by using lithium aluminum hydride^(119a) and then reacted *via* two paths. The first reaction was done by the Vilsmeier formylation reaction using POCl_3 and DMF. One unanticipated finding was that the sole formation of *N*-methyl-3-formyl-2-chloromethyl indole **215** was observed. While, the second reaction involved the formylation reaction of **214**. Two methodologies were employed to afford 2-(*N*-methyl)indolylmethylacetate **216**, where no significant difference was found when lithium chloride catalysed the acetylation of **214** in the presence of acetic anhydride. While a good result was obtained, compound **214** was treated with triethylamine, acetic anhydride and 4-(dimethylamino)pyridine (DMAP)-promoted acetylation.^(119b) ^1H and ^{13}C NMR on this material (**216**) confirmed the disappearance of the alcohol signal and presence of signals due to acetyl group, with peaks at 1.99 ppm (3H, s, COCH_3) and 171.54 ppm (COCH_3) observed (Scheme 68). Following the success of these reactions, *N*-methyl-3-formyl-2-indolylmethylacetate **217** was synthesised from the reaction of **216** with POCl_3 with a 55% yield.



Scheme 68: The synthesis of aldehydes **215** and **217** *via* Vilsmeier formylation: (i) LiAlH_4 , dry THF, -10°C to rt, 5-10 min; (ii) POCl_3 , DMF, rt (30 min), then 60°C , 24 h; (iii) acetic anhydride, Et_3N , DMAP, ether, rt, 24 h; (iv) LiCl , acetic anhydride, rt, 24 h, no reaction; (v) POCl_3 , DMF, rt (30 min), then heating at 60°C , 3 h.

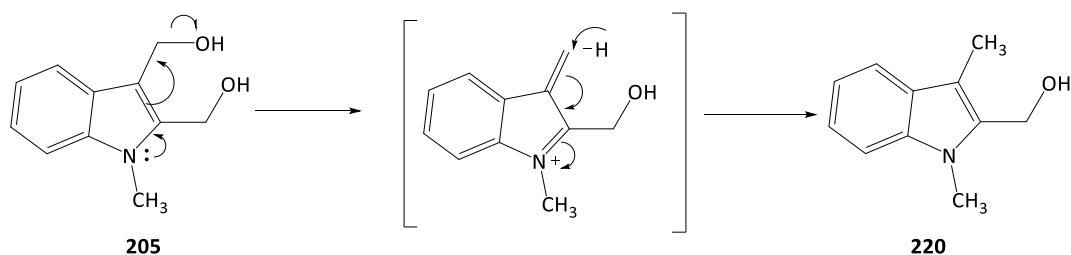
Various indole derivatives have been used as starting materials in reduction reactions using LiAlH_4 as a powerful reductant. In the literature, different authors have reported the synthesis of desired diols at a variety of temperatures (0°C conditions to 70°C conditions). In this work, the successful methodology employed to synthesised diols chemoselectively used LiAlH_4 at -10°C conditions with a suitable workup. The results in Scheme 69 shows two substrates namely, methyl-*N*-methyl-2-indole carboxylate **212** and methyl-3-formyl-1-methyl-2-indole carboxylate **213**, which were reacted with LiAlH_4 under -10°C in dry THF,^(120a) and *N*-methyl-3-formyl-2-indolylmethylacetate **217** was reacted with NaBH_4 at $0-5^\circ\text{C}$. However, this reaction proved to be unsuccessful as no reaction occurred. In terms of **214**, the successful reduction reaction was obtained in 90% yield where NMR analysis confirmed the conversion of **212** into **214**. It was noted that ^{13}C -NMR analysis showed the singlet peak at $\delta = 4.74$ ppm (57.55) is related to methylene group (a) in **214**, as shown in Scheme 69.^(120a) Many attempts were tried to reduce *N*-methyl-3-methanol-2-indolylmethylacetate **217** to *N*-methyl-3-methanol-2-

indolylmethyl-acetate **219** by reaction with NaBH_4 in methanol at 0-5 °C, but unfortunately no product was observed from this starting material. Analysis of this crude mixture by NMR revealed that starting material **217** was decomposed before the reaction workup.



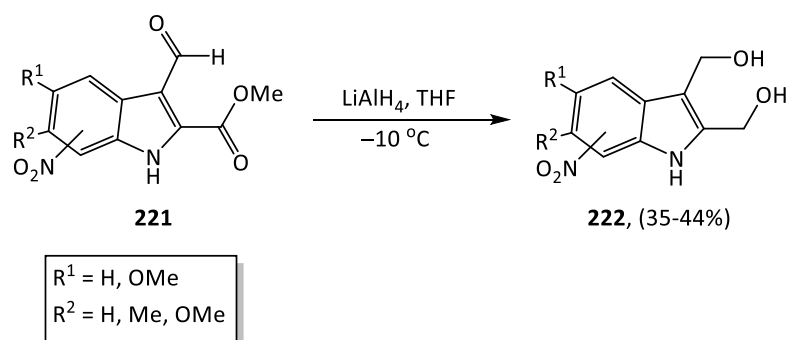
Scheme 69: The reduction reaction of **212**, **213** and **217**

The attempted synthesis of diol **205** has been shown to be critical due to its decomposition through chromatographic purification. Therefore, it was found that a disappointing yield was obtained from this reaction despite the formation of the desired product **205**. It was formed in 40% yield with the appearance of diol peaks at 1.98 (s, 1H, **d**), 2.6 (s, 1H, **b**), 4.82 (s, 2H, **c**) and 4.87 (s, 2H, **a**) ppm, as depicted above in Scheme 69. Therefore, reduction of **213** to **205** proved to be more difficult than initially anticipated. A possible explanation for this result may be the synthesis of the undesired 3-methyl indole derivative **220**. This was proposed to occur from the over-reaction of the initial product, as shown in Scheme 70.^(120a)



Scheme 70: The predicted mechanism of diol over-reaction

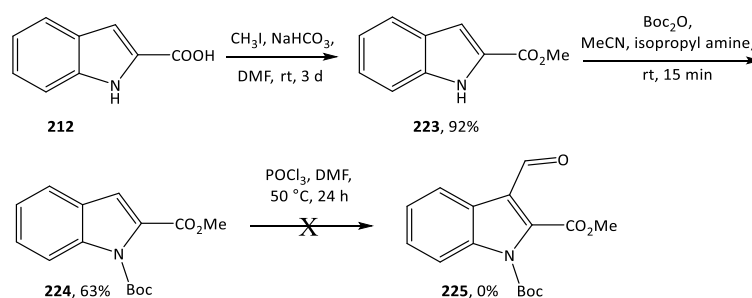
Indeed, this investigation is consistent with the findings of Skibo and Xing (2001) who showed that the selective reduction of 2,3-dicarbonyl indoles **221** is possible (Scheme **71**), but that yields are often low.^(120b)



Scheme 71: The Synthesis of 2,3-dihydroxy methyl indole derivatives

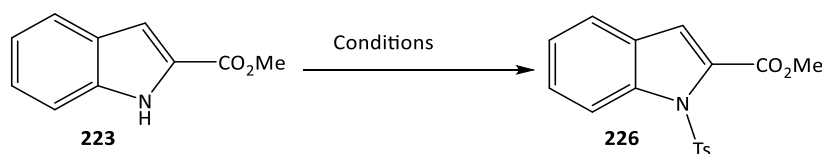
At first glance, a synthetic route for preparing the compound **223** uses methyl iodide as a methylating agent with indole-2-carboxylic acid **212** yielding in 92% yield. Next, substrate **224** was synthesised with an electron withdrawing protecting group (Boc) from methyl-2-indole-carboxylate **223**. In terms of **224**, treatment of **223** with di-*tert*-butyl dicarbonate (Boc_2O) in acetonitrile yielded the corresponding ester **224** where, consistent with findings by Freed *et al*,⁽¹²¹⁾ the signals at 1.55 ppm (s) and 3.84 ppm (s) could be assigned to three methyl groups [$-(\text{CH}_3)_3$] and ester group ($-\text{OCH}_3$). However, regarding the formylation

reaction of **224** into **225**, there was an unexpected result, no reaction was observed (Scheme 72).



Scheme 72: The synthesis of methyl-3-formyl-*N*-(*tert*-butyloxycarbonyl)-2-indole carboxylate **225**

As the use of Boc as a protective group had not proved to be a useful improvement in this project, the next step was to find of alternative protecting groups. The compound **226** was prepared by adapting the procedure used by Kerr and Karadeolian (2010).⁽¹²²⁾ In particular, the synthesis of **226** was problematic in terms of its yield. At first glance, many attempts were employed through the use of different equivalents of each component in this reaction (Table 4).

Table 4: Attempts of tosylation reaction by TsCl using different bases

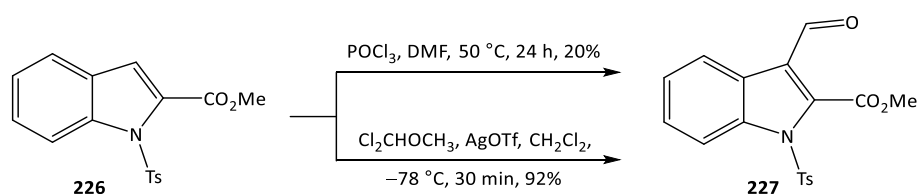
Run ^[a]	223 (eq.)	TsCl (eq.)	Base (eq.)	Solvent	226%
A	1	1.3	NaH (1.3)	DMF	33
B	1	2.2	NaH (1.3)	DMF	0
C	1	1.8	K ₂ CO ₃ (2.9) ^[b]	pentanone	0
D	1	2.0	NaH (1.3)	DMF	21
E	1	1.1	Tbhs (0.07) ^[c]	CH ₂ Cl ₂	0

[a] **A**, **B**, and **D** reactions were carried out in DMF, stirring for 24 hours at room temperature (rt) **[b]** **C** reaction was done at reflux for (4-24 h) **[c]** **E** reaction was carried out at rt with stirring for 24 h using tetrabutylammonium hydrogensulfate (Tbhs) in CH₂Cl₂.

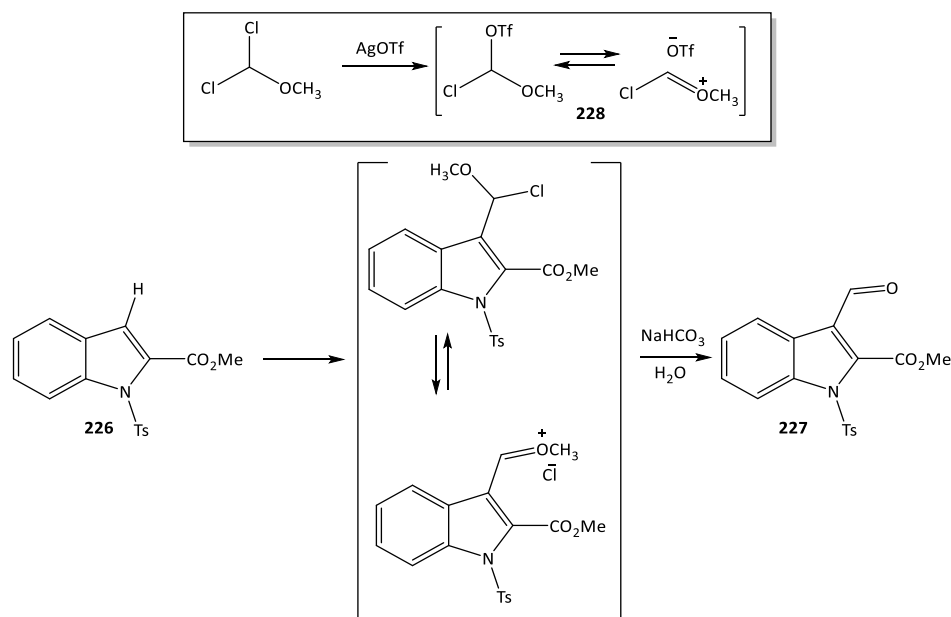
It can be seen from the data in Table 4 that, the method **A** worked better than the other different conditions. No reaction was detected when methods **B**, **C** and **E** used. This outcome is contrary to that of Lindsey *et al* (2007) who reported a wonderfully efficient methodology.⁽¹²³⁾

As mentioned before, the Vilsmeier formylation reaction is a typical approach to gain the desired aldehydes. Two strategies were employed to synthesise **227** from **226**. First, the synthesis commenced with the key formylation reaction⁽¹¹⁷⁾ according Bennasar's methodology, where the transformation of methyl *N*-tosyl-2-indole carboxylate **226** into methyl-3-formyl-*N*-tosyl-2-indole carboxylate **227** was disappointing, proceeding in just 20% yield. This result corroborated the ideas of Kehler *et al* (2010), who suggested that it was difficult to formylate tosylated indole products, so it was necessary to

detosylate these substrates prior to the Vilsmeier formylation reaction.^(124a) Meanwhile, an alternative method was applied by using a AgOTf-promoted formylation reaction,^(124b) using dichloromethyl methyl ether ($\text{Cl}_2\text{CHOCH}_3$) as the formylating reagent.⁽¹²⁵⁾ For the synthesis of **227**, dichloromethyl methyl ether was added to a cooled solution of **226** in dichloromethane, followed by added silver triflate to afford exclusively methyl-3-formyl-*N*-tosyl-2-indole carboxylate **227** in 92% yield (Scheme 73). However, this method is still not ideal given the high cost of the starting materials.



Scheme 73: The synthesis of methyl-3-formyl-*N*-tosyl-2-indole carboxylate **227**. The proposed formylation mechanism would proceed *via* the reaction pathway with AgOTf shown in Scheme 74. Initially, activation of dichloromethyl methyl ether ($\text{Cl}_2\text{CHOCH}_3$) by AgOTf may occur, leading to a highly active intermediate **228**. Nucleophilic addition of indole to **228** preferentially at the position 3, followed by hydrolysis would provide the corresponding aldehyde **227**. Although highly acidic trifluoromethanesulfonic acid is generated under the reaction conditions, the formylation of indoles is tolerated under the low reaction temperature (-78 °C).^(124b)

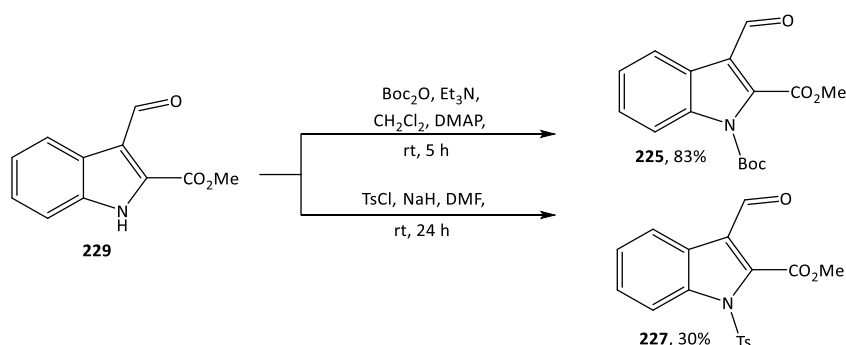


Scheme 74: The feasible mechanism of the AgOTf-promoted formylation reaction

¹H-NMR analysis of the product **227** revealed that it had a signal at 10.13 ppm (1H, s) is attributed to aldehyde proton, while peaks at 2.38 ppm (3H, s) and 4.11 ppm (3H, s) belonging to the (Ar-CH₃) and (O-CH₃) groups respectively.

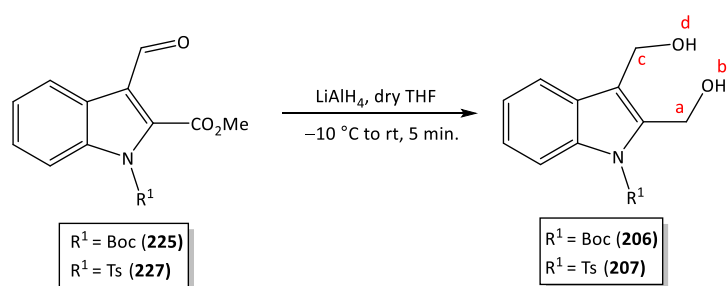
Another approach to the synthesis of **225** and **227** from **229** has been investigated as shown in Scheme **75**. It was decided to alter the sequence of the reactions and carry out the formylation of **223** followed by protection. The Boc protecting reaction with **229** appeared extremely successful, 83% conversion into the product **225** being observed when it is performed in the presence of DMAP with di-*tert*-butyl dicarbonate (Boc₂O) in dichloromethane. ¹H-NMR on **225** confirmed the appearance of the signal due to the carbonyl group of aldehyde at 10.21 ppm (1H, s) and the likely introduction of a new substituent (Boc group) at 1.67 ppm (9H, s). However, the unsuccessful tosylation transformation of **229** into **227** was observed. This reaction was also disappointing however; after 24 hours, and many attempts, only 30% total

conversion was obtained where a mixture of both tosyl chloride and starting material **229** was present as well.



Scheme 75: The protection of the formylated **229**

After the disappointing synthesis of diols **219** and **205**, examination of the synthesis of alternative diols which have *N*-protective groups instead of the methyl group was the next objective. It was anticipated that the electron withdrawing protecting group would prevent overreduction. Thus, with methyl 3-formyl-1-(*tert*-butoxycarbonyl)-1H-indole-2-carboxylate **225**, and 3-formyl-methyl *N*-tosylindole-2-carboxylate **227**, the performance of these compounds in reduction reaction was examined (Scheme **76**, Table 5).

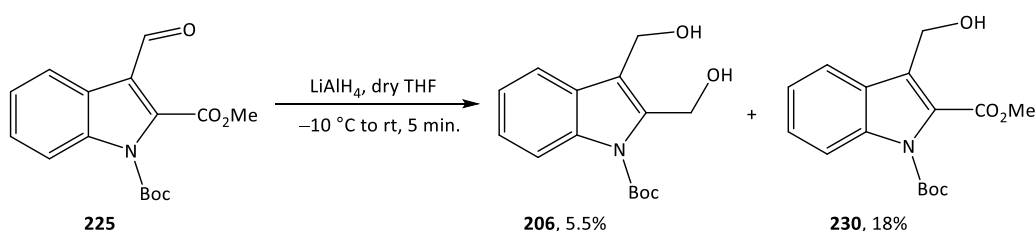


Scheme 76: The reduction reaction of **225** and **227** by LiAlH_4

Table 5: Using different reducing agents for the synthesis of diols

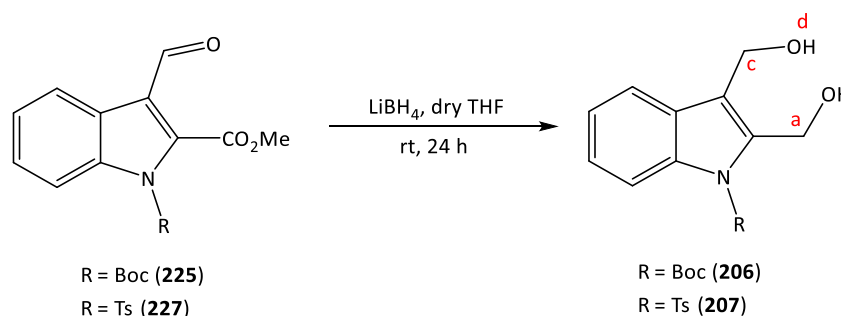
Entry	SM	Reduction agents			Products
		LiAlH ₄ Yield%	LiBH ₄ Yield%	DIBAL Yield%	
1	225	5.5 (– 10 °C)	46	0	206
	225	11 (70 °C)	0	0	206
2	227	0	71	0	207

The initial reaction with compound **225** and LiAlH₄ was low yielding with 5.5% conversion into the product *N*-(*tert*-butoxycarbonyl)-2,3-bis(hydroxymethyl)indole **206** being observed at –10 °C. However, upon heating at 70 °C, this was slightly improved to 11%. The most striking result to emerge from the data is that the formation of an unexpected product from this reaction (Scheme 77); this is consistent with the ester substituent not being reduced by LiAlH₄,^(120a) with 18% of this side-product (1-(*tert*-butyl)-2-methyl-3-(hydroxymethyl)-1H-indole-1,2-dicarboxylate **230**) isolated by chromatography. Furthermore, the use of diisobutylaluminum hydride solution (DIBAL) afforded a disappointing result as a reducing agent with **225**.



Scheme 77: The synthesis of side-product **230** from the nonselective reduction LiBH₄ was next tested as an alternative reducing agent. The reaction of lithium borohydride with methyl 3-formyl-1-(*tert*-butoxycarbonyl)-1H-indole-2-carboxylate **225** led to a significant improvement; *N*-(*tert*-butoxycarbonyl)-

2,3-bis(hydroxymethyl)indole **206** was isolated in 46% yield, as shown in Scheme 78. The NMR spectra showed that the hydroxyl groups were present as well as the methylene groups being shielded and observed at $\delta = 2.10$ ppm (br.s, 1H, **b**), 3.99 ppm (s, 1H, **d**), 4.85 ppm (s, 2H, **a**), and 4.90 ppm (s, 2H, **b**) respectively. In addition, three methyl group that are related to (Boc) group were observed at $\delta = 1.75$ ppm. This successful methodology was then extended to the synthesis of *N*-(toluene-4-sulfonyl)-2,3-bis(hydroxymethyl)indole **207** from 3-formyl-methyl *N*-tosylindole-2-carboxylate **227** where the hydroxyl and methylene groups were observed at $\delta = 1.61$ ppm (s, 2H, **d, b**), 4.84 ppm (s, 2H, **a**), 4.98 ppm (s, 2H, **c**) in 71% yield respectively (Scheme 78).



Scheme 78: The reduction reaction of **225** and **227** by LiBH_4

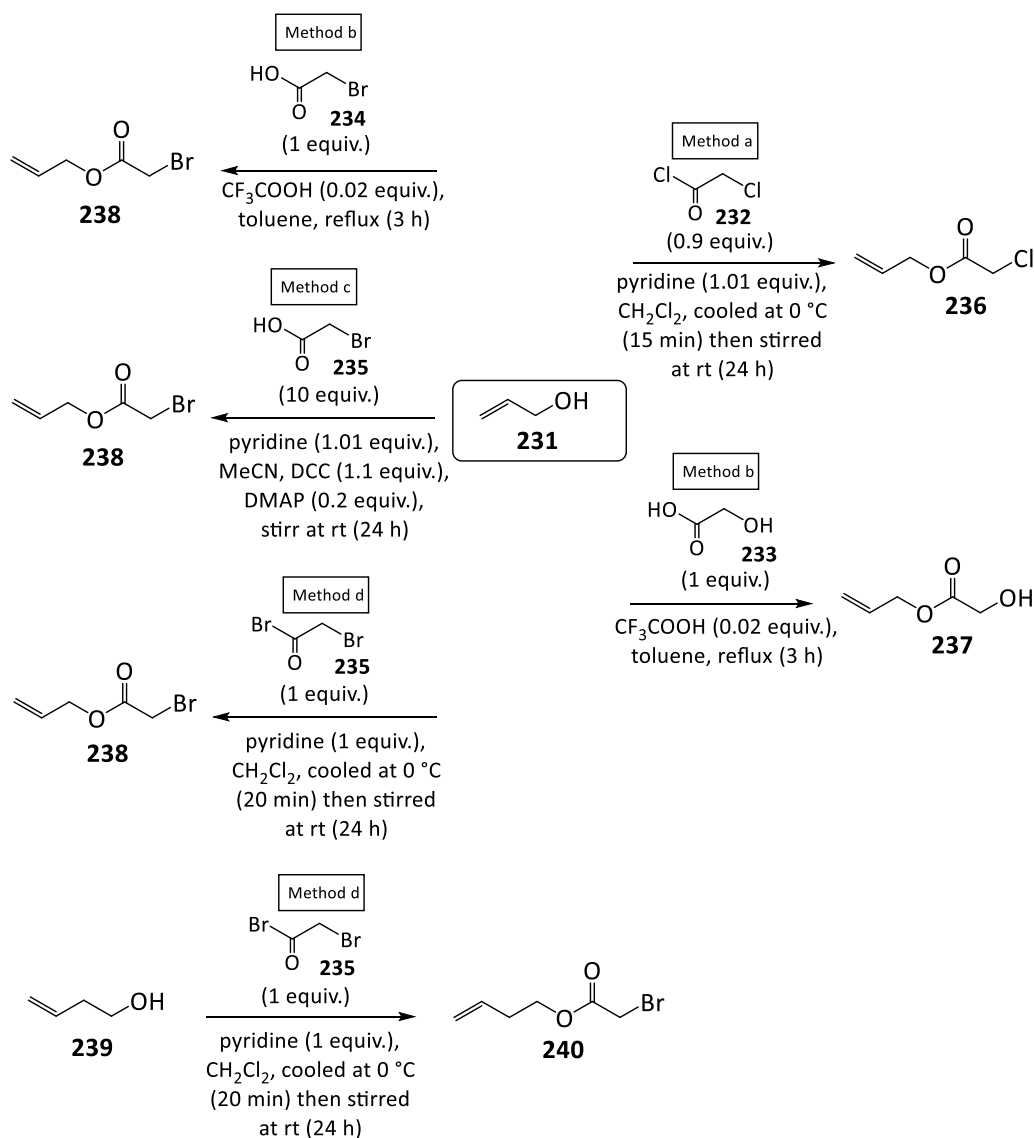
2.4 Preparation of phosphorane ylides

To test the proposed 6π -electrocyclisation/Diels-Alder methodology it was necessary to prepare phosphorane ylides with an appended alkene group.

All halides required for the synthesis of phosphonium salts in this chapter were prepared *via* a range of approaches. Four types of 2-haloacetyl-allyl esters (Scheme 79, Table 6) were prepared *via* amidation under basic conditions⁽¹²⁶⁾ as well as acidic Fischer esterification⁽¹¹⁴⁾ by acid. The 45-50% yields of entries

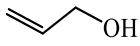
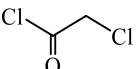
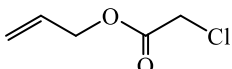
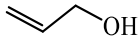
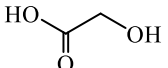
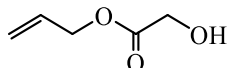
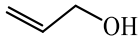
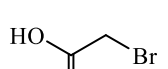
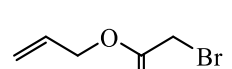
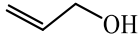
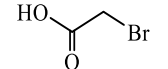
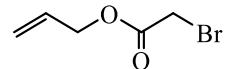
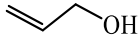
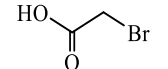
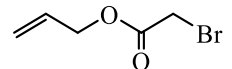
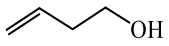
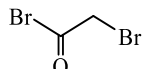
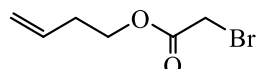
(**1-3**) were slightly low due to the extraction solvent, utilising acids such as (H_2SO_4 , CH_3COOH , CF_3COOH) and a dehydration step that occurs in the reaction.

Entries **3-6**, three methods under different conditions were employed to synthesise allyl esters **238** and **240** from allyl alcohol **231** and 3-butenyl alcohol **239** respectively. It was found that the Fischer esterification by using acetic acid as well as using DCC and DMAP in acetonitrile gave reasonable yields of entries **3** and **4**. However, a substantially better catalyst for the synthesis of **238** and **240** proved to be pyridine (Table 6, entries **5** and **6**), which gave in 100% and 88% yield in dichloromethane respectively.⁽¹²⁷⁾ The synthesis of each of these esters was evident from the characteristic alkene peaks in the ^1H -NMR. It was immediately clear that the methyne (CH) proton displays a characteristic ddt signal between 5.80-6.00 ppm e.g. entry (**1**), 5.93 ppm for entry (**2**), 5.88 ppm for entries (**3-5**) and multiple peaks at 5.74-5.84 ppm for entry (**6**).



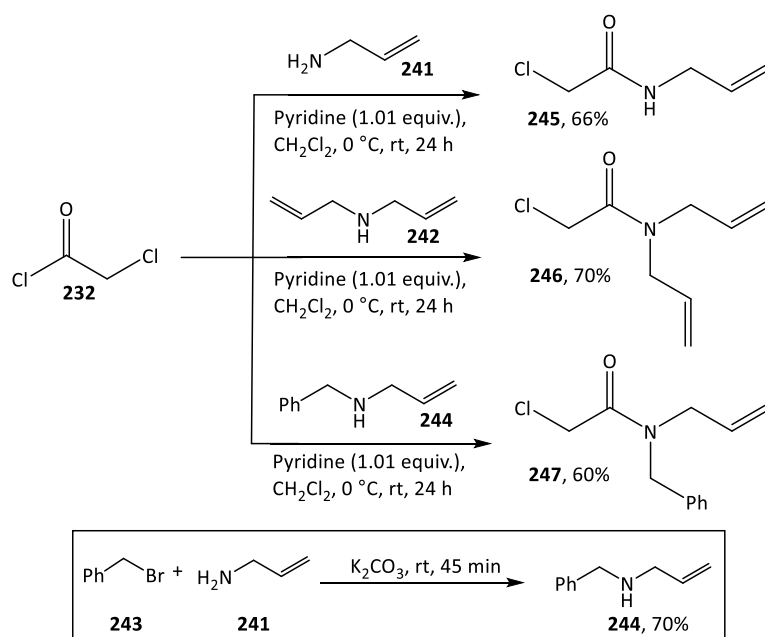
Scheme 79: Preparation of allyl esters derived from allyl alcohol **231** and 3-butenyl alcohol **239**

Table 6: Preparation of allyl esters derived from allyl alcohol **231** and 3-butenyl alcohol **239**

Entry	Halo compounds		Product	Yield%	Catalyst
1				50	Base ^a pyridine
2				45	Acid ^b CH ₃ COOH
3				45	Acid ^b CF ₃ COOH
4				40	DCC, DMAP in MeCN ^c
5				100	Base ^d pyridine
6				88	Base ^d pyridine

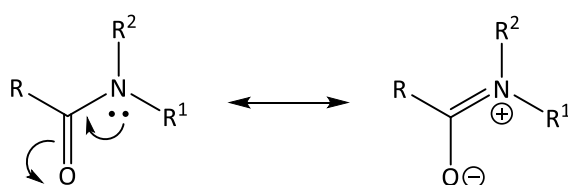
a) Prepared according to Evans *et al.*⁽¹²⁶⁾, b) Prepared according to Bailey and co-workers ⁽¹¹⁴⁾; c) Reaction was carried out on *N,N'*-dicyclohexylcarbodiimide (DCC) (1.1 equiv.) and DMAP (0.2 equiv.) in acetonitrile ⁽¹²⁷⁾; d) Prepared according to Anderson *et al.*⁽¹²⁸⁾

Furthermore, the preparations of *N*-allyl chloroacetamide **245**, *N,N*-diallyl chloroacetamide **246**, and *N*-allyl-*N*-benzyl chloroacetamide **247** were achieved by adapting literature method for the general preparation of amides by using Evans's protocol (Scheme **80**).⁽¹²⁶⁾



Scheme 80: The synthesis of allyl amides derived from chloroacetyl chloride and allyl amines

NMR analysis of **246** clearly showed standard peaks for allyl and methyl groups and no evidence to suggest the presence of rotamers. However, the diagnostic proton NMRs compounds (**245** and **247**) were more complicated due to the presence of amide rotamers. Rotamers are conformational isomers and are not resolved on the NMR timescale due to restricted rotation about the C-N bond as a result of delocalisation of the N lone pair into the carbonyl (Scheme 81).



Scheme 81: Representation of the amide rotamers

It can be seen from the data in Figure 10 that the ¹H-NMR spectrum of compound **245** presented duplicated signals for each NH, COCH₂-. In terms of

allyl amide **245**, the multiplet signal of $\text{-NHCH}_2\text{-}$ was present to a lesser extent at 3.75-3.80 ppm for both minor and major rotamers. Meanwhile, the -NH showed two signals at 5.19 ppm (s, major) and 5.20 ppm (s, minor). In contrast, the doublet signals for the allyl $\text{-NCH}_2\text{-}$ of **247** refers to 3.89 ppm and 4.01 ppm for the major and minor rotamers. Additionally, the multiplet peak of 4.57-4.60 ppm assign the signal of $\text{-CH}_2\text{-}$ on position 6. These results confirmed the presence of rotamers.

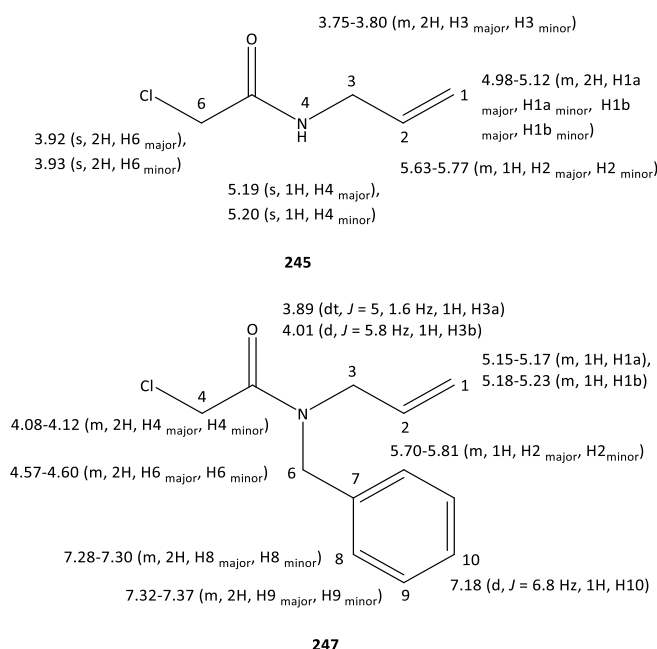
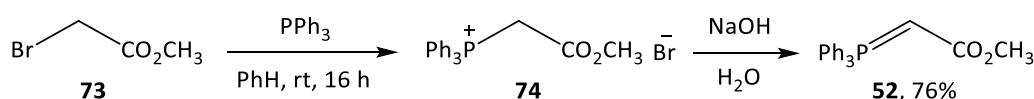


Figure 10: ^1H -NMR signal duplications and other NMR details of **245** and **247**

The next step was the preparation of phosphonium salts from these compounds. The required phosphonium salts were prepared by reaction of triphenylphosphine and the required halo ester or amide compounds using the ‘salt-method’ *via* $\text{S}_{\text{N}}2$ substitutions. This is in fact a two-step process which involves initial synthesis of the phosphonium salt from phosphine and the requisite halo esters amide compounds, then a subsequent deprotonation step to form the resulted ylide. The key to this strategy is the strength of base used

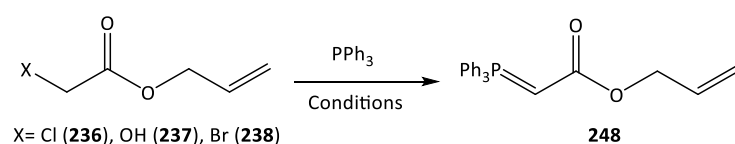
and this obviously depends on the CH acidity of the phosphonium salt conjugate acid. As firstly noted by Michaelis and Gimborn (1984)⁽¹²⁹⁾ the use of stabilised ylides (salt $pK_a \sim 9$) can be reacted successfully with bases such as hydroxide or alkoxide compared with unstabilised ylides (salt $pK_a \sim 22$), which require stronger bases such as alkyllithiums.⁽¹³⁰⁾ Scheme 82 shows two-step overall process for the synthesis of methyl (triphenylphosphoranylidene)acetate 52 affording a 76% yield of the product.^(34a)



Scheme 82: The ‘salt method’ for the preparation of ylides

In most cases the ‘phosphonium salts’ were not solids as expected, but proved to be a hygroscopic syrup, hence, they could not be crystallised or purified, but it was found that this material could be carried through to the next stage without further purification to synthesise the desired ylides. The resulting phosphonium salts from the reaction of allyl ester and allyl amide failed based on the ^1H -NMR analysis of the corresponding salts, which did not show any peak related to the allyl group. Running the $^{31}\text{P}\{^1\text{H}\}$ -NMR for the entry (1 and 2, Table 7) there were two peaks at -5.95 ppm and 20.83 ppm that related to Ph_3P and a phosphonium salt, but not the one that was desired. The product could not be identified spectroscopically hence, no attempt was made to identify this undesired phosphonium salt. To the best of our knowledge, there is no literature evidence regarding the decomposition of allyl ester ylides (or

their phosphonium salts) but it is possible that triphenylphosphine attacks the allyl ester group rather than the bromoalkane respectively. As can be seen from the Scheme 83 and Table 7, neither different solvents nor leaving groups worked. These reactions were all repeated several times to confirm that it was the procedure rather than experimental error that was the problem. These results suggest that trying different starting materials and conditions could be useful to synthesise the desired phosphorane ylides by using the salt method.^(34a)



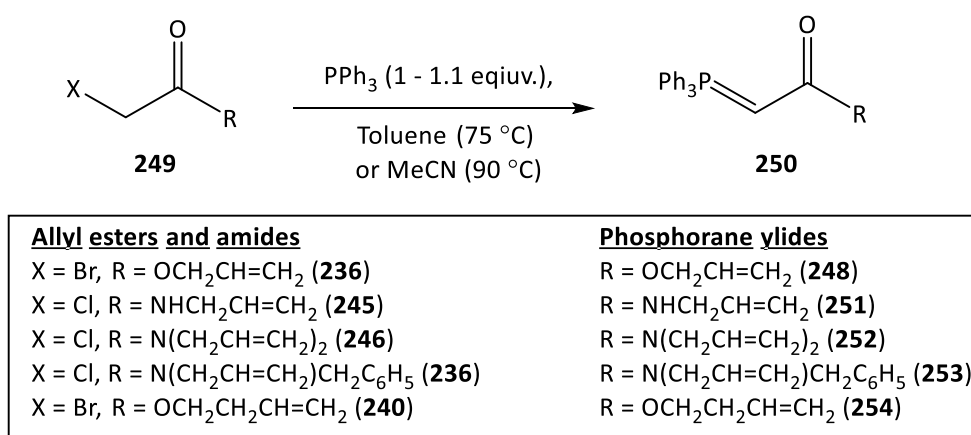
Scheme 83: The unsuccessful synthesis of phosphorane ylide **248**

Table 7: The unsuccessful synthesis of phosphorane ylide **248**

Entry	Halo compounds	PPh ₃ (equiv.)	Conditions/ 24 h
1	 236	1.2	Toluene, rt
			MeCN, 50 °C
2	 238	1.1	Toluene, rt
			Toluene, 130 °C
3	 237	1.1	TFA, 55 °C
4	 238	1.02	MeCN, 90 °C
			MeCN, 130 °C

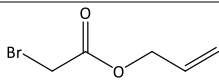
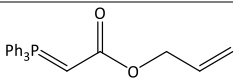
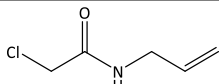
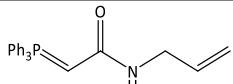
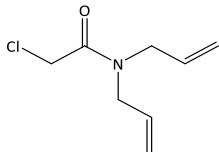
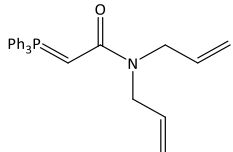
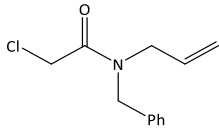
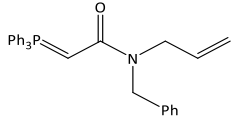
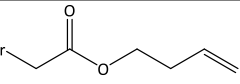
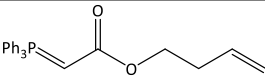
The experiments above showed that the preparation of allyl ester ylides was unsuccessful, so other starting materials with allyl amides was attempted instead, as illustrated in Table 8. The resulting phosphonium salt and the compounds were checked for success by $^{31}\text{P}\{^1\text{H}\}$ -NMR. The key signals of entries 3-5 in the $^{31}\text{P}\{^1\text{H}\}$ -NMR data were between 17.7 (s) ppm to 24.9 (s) ppm. The proton NMRs of these compounds proved to be complicated due to the presence of rotamer forms that are not resolved on the NMR timescale due to restricted rotation about the C-N and C-O bonds, as shown above in Scheme 81.

The successful results obtained from the preliminary synthesis of phosphorane ylides, are summarised in Scheme 84 and Table 8.



Scheme 84: The synthesis of phosphorane ylides

Table 8: The synthesis of phosphorane ylides

Entry	Halo compounds	PPh ₃ (equiv.)/ conditions/24 h	Ylides/%
1^a	 236	1.0/Toluene 75 °C	 248, 70
2^b	 245	1.02/MeCN 90 °C	 251, 0
3^b	 246	1.02/MeCN 90 °C	 252, 65
4^c	 247	1.1/MeCN 90 °C	 253, 34
5^a	 240	1.0/Toluene 75 °C	 254, 70

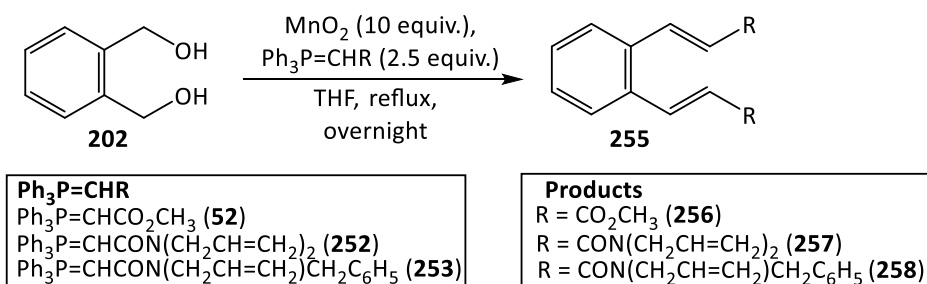
(a) Prepared according to Shan and co-workers procedure;⁽¹³¹⁾ **(b)** Prepared according to Lang and co-workers using the salt method;⁽¹³²⁾ **(c)** Prepared according to Jones and co-workers.⁽¹³³⁾

The identity of ylides and their successful formations could be determined by the signal from the key methyne proton. In each case, a ¹H doublet with a ²J_{PH} coupling of ~ 22 Hz was observed.

2.5 TOP experiments towards trienes

Tandem oxidation process (TOP) is important for a wide range of scientific and industrial processes where it constitutes a novel methodology to synthetic organic chemistry.

The first TOP reactions were undertaken with diol **202** methyl ester ylide **52**, **252** and **253** (Table 9, Scheme 85). Initially, the reaction was investigated using a standard MnO₂ mediated TOP reaction with three phosphoranes (methyl (triphenylphosphoranylidene) acetate **52**, *N,N*-diallyl(triphenylphosphoranylidene) acetamide **252** and *N*-allyl-*N*-benzyl (triphenylphosphoranylidene) acetamide **253**. Heating benzene-1,2-dimethanol **202** with (10 equiv.) of MnO₂ and (2.5 equiv.) of phosphoranes led to the synthesis of the desired trienes; this constituted a general procedure for all TOP reactions attempted in this chapter. In the ¹H-NMR analysis, it was satisfying to observe that these reactions were successful; 50% of (2*E*,2'*E*)-dimethyl-3,3'-(1,2-phenylen)diacrylate **251** was obtained. However, it was noted that (*E*)-3-{o-[(*E*)-3-(diallylamino)-3-oxo-1-propenyl]-phenyl}-1-(diallylamino)-2-propen-1-one **252** and (*E*)-3-{o-[(*E*)-3-[(benzyl)-*N*-allylamino]-3-oxo-1-propenyl]phenyl}-1-[(benzyl)-*N*-allyl-amino]-2-propen-1-one **253** existed as a 5.5:1 and 1.2:1 mixture of isomers in solution respectively.



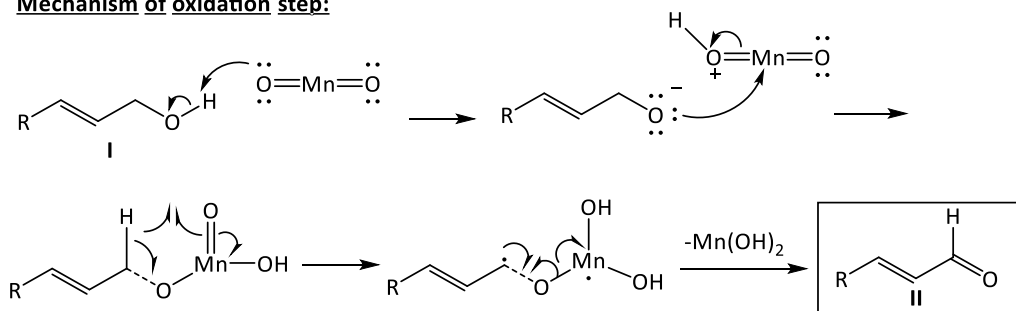
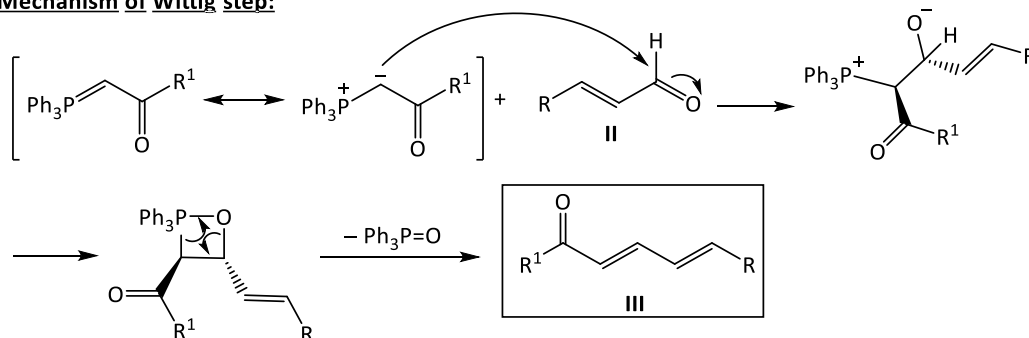
Scheme 85: Initial TOP reaction of benzene-1,2-dimethanol **202**

Table 9: Initial TOP reaction of benzene-1,2-dimethanol **202**

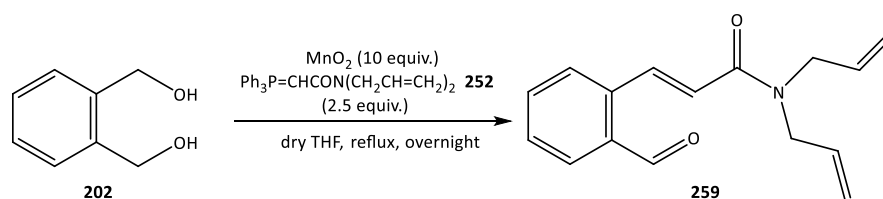
Entry	Phosphorane/ R	[255]/ Yields%
1	CO_2CH_3 52	<p>256, 50%</p>
2	$\text{CON}(\text{CH}_2\text{CH}=\text{CH}_2)_2$ 252	<p>257, 40%</p>
3	$\text{CON}(\text{CH}_2\text{CH}=\text{CH}_2)\text{CH}_2\text{C}_6\text{H}_5$ 253	<p>258, 35%</p>

The identity of the product was shown by the presence of the key alkene signals in the ^1H -NMR data. Doublets ($J = 15.4$ Hz) were observed at 7.99 ppm for the major rotamer and 8.43 ppm for the minor rotamer for **257** and 8.48 ($J = 15.2$ Hz) for both minor and major rotamers for **258**.

Mechanistically, the general reaction initiates with the oxidation step of alcohol **I** into the aldehyde **II** using manganese dioxide (MnO_2) in THF, and then this aldehyde converted to the desired alkene **III** *via* Wittig reaction (Scheme **86**).

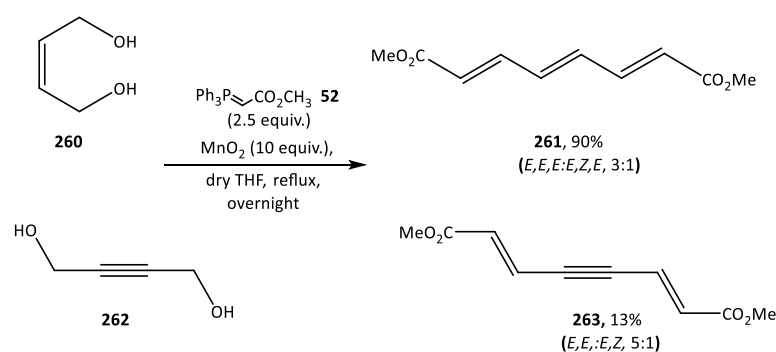
Mechanism of oxidation step:**Mechanism of Wittig step:****Scheme 86:** General mechanism of TOP reaction

These yields are slightly misleading, some of the diols, for example **257**, underwent incomplete oxidation and Wittig reaction to prepare aldehyde **259** (Scheme **87**). The single most striking observation to emerge from the data comparison was only low yield of the triene **257**. Instead, these reactions produced high yields of the starting material (aldehyde **202**) and used ylide **252**, where, the oxidation step precedes the mono-oxidised product **259** as an unexpected product, presumably the increased steric bulk the second olefination step. This observation confirmed the lower yield of triene **257**. NMR analysis of **259** gave obvious peaks at 6.67 ppm ($J = 15.8$ Hz) and 8.42 ppm ($J = 16.1$ Hz) that related to alkene group resulting from the TOP reaction. While the key signal of aldehyde peak was present at 10.37 ppm that proved this structure **259**.



Scheme 87: Unexpected side product **259** from TOP reaction

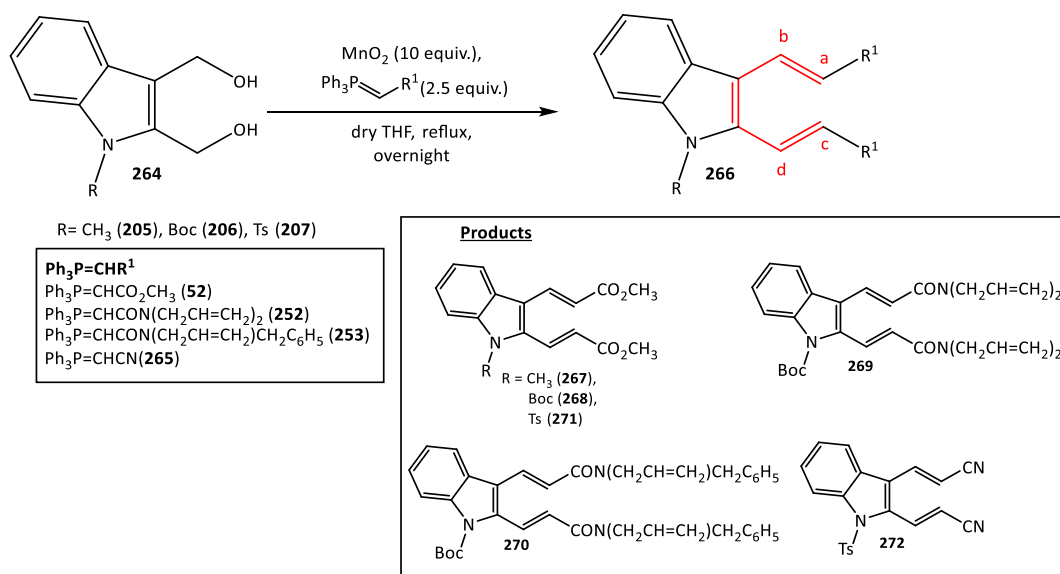
In addition to benzene-1,2-dimethanol **202**, unsaturated diols such as (Z)-2-butene-1,4-diol and 2-butyne-1,4-diol were also used. The reaction with the methyl ester ylide **52** shows an excellent yield in terms of **261** in a 90% yield and a 3:1 ratio of (*E,E,E*:*E,Z,E*) isomers. Although the TOP reaction still occurs, it is less significant than that observed with **202**; a 13% yield of **263** was obtained following chromatography, as shown in Scheme **88**.



Scheme 88: TOP reaction of unsaturated diols by MnO_2

The analysis of trienes was particularly problematic due a mixture of isomers being obtained. Reasonable yields were obtained *via* TOP reaction of diols, regardless of terminal substituent (R) in indole system (Scheme **89**). The results obtained from the preliminary analysis of ‘triene’ indoles can be compared in Scheme **89** and Table **10**. Initial attempts to perform the TOP reaction of entries **4** and **6** were unsuccessful, with a complex mixture of compounds obtained.

The ^1H -NMR analysis of these crudes products proved the presence of complex mixture of starting material with 'triene' indoles (product). It is somewhat surprising that no **270** and **272** compounds were synthesised from this reaction, as illustrated in Table **10**, where it was noted the decomposition of those products. This was observed many times *via* the purification step using column chromatography. To circumvent this problem, preparative TLC was instead used. This initiative proved again unsuccessful and gave decomposed material (pink solid). On the other hand, entries **1-3** and **5** gave modest yields after purification. NMR analysis confirmed the appearance of alkene protons of 'triene'. For example, ^1H -NMR spectroscopy of **267** showed 6.25 ppm (d, $J = 16$ Hz, **c**), 6.50 ppm (d, $J = 16$ Hz, **a**), 7.82 ppm (d, $J = 16$ Hz, **b**) and 7.93 ppm (d, $J = 16$ Hz, **d**) ppm. In terms of **268** and **269**, four doublet protons that related to the alkene appeared in the range 6.08-8.25 ppm. Meanwhile the structure of **271** was confirmed by the appearance of doublet protons at 6.06 ($J = 15.8$ Hz, **a**), 6.57 ($J = 16.2$ Hz, **c**), 7.60-7.62 (m, **d**), 8.31-8.35 (m, **b**) ppm, as illustrated in Scheme **89**.



Scheme 89: Preparation of alternate 'triene' indoles

Table 10: Preparation of alternate 'triene' indoles

Entry	R	R ¹	Products/ [266]	Yield%
1	CH ₃	CO ₂ CH ₃ 52	267	19
2	Boc	COCH ₃ 52	268	18
3	Boc	CON(CH ₂ CH=CH ₂) ₂ 252	269	29
4	Boc	CON(CH ₂ CH=CH ₂)CH ₂ C ₆ H ₅ 253	270*	0
5	Ts	CO ₂ CH ₃ 52	271	51
6	Ts	CN 265	272*	0

*

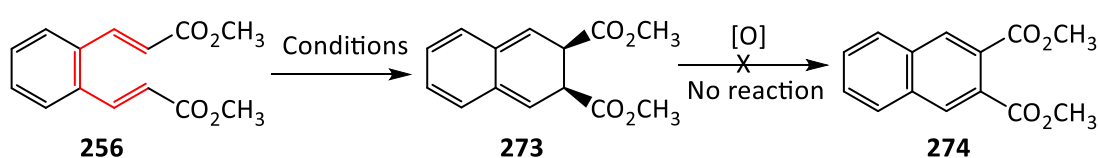
Decomposed on silica

In summary, these results show that the possible of employment TOP reactions for the synthesis of triene despite the difficulties that have faced in this work and the ability of purification of these products using different eluents. The next step will be the 6 π -electrocyclisations of these trienes using microwave irradiation.

2.6 Photochemical and thermal electrocyclisations

As mentioned in the first chapter, the formation of cyclohexa-1,3-dienes system has been proposed in the biosynthesis of natural products *via* a disrotatory electrocyclisation of 1,3,5-hexatrienes which is considered an important process, particularly in this project. Generally, this cyclisation is classified into two categories; thermal and photochemical electrocyclisations. Thermal cyclisation typically requires high temperatures between 150 to 200 °C which are necessary to close the triene ring, while photochemical cyclisation undergoes a conrotatory cyclisation mode according to the Woodward-Hoffmann rules.

Although part of the conjugated 6π -system is embedded into the aromatic benzene ring the ease of preparing the substrates **256** made it a good starting point. Two approaches were attempted with the 'triene' (Table **11**, Scheme **90**). It was anticipated that the presence of O₂ in the atmosphere / solvent would be sufficient to oxidise the diene if it did form.



Scheme 90: 6 π -electrocyclisation reaction of **256**

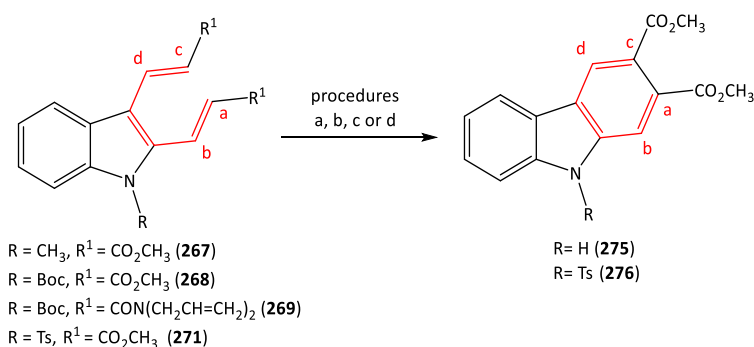
Table 11: Conditions of electrocyclisation reaction

Conditions	MnO ₂	Result
Thermal, Ph ₂ O, 250 °C	-----	No reaction
Thermal, Ph ₂ O, 250 °C	50 equiv.	No reaction
Microwave, toluene, 175 °C	-----	No reaction
Microwave, toluene, 175 °C	50 equiv.	No reaction

Thermolysis of triene **256** in diphenyl ether (boiling point 258 °C) led to no reaction and the starting material was recovered along with small amounts of decomposition. Similarly, microwave irradiation at 175 °C in toluene had no effect on the substrate, no reaction being achieved. Both reactions were repeated with 50 equiv. of MnO₂ added to act as the oxidant, shown in Table **11** above. Wangelin and co-workers have previously shown that MnO₂ can aromatise cyclohexadienes.⁽¹³⁴⁾ Unfortunately the addition of MnO₂ to promote the oxidation had no effect. Given the high energy barrier to reaction that would be involved in the aromaticity, the failure of this reaction was unsurprising. Though the triene **256** had previously been cyclised under photochemical promotion, no thermal reactions have been shown at this stage, and no photochemical reactions were attempted. Meanwhile, with the substrates **257** and **258**, the 6 π -electrocyclisations were attempted. Thermolysis of **257** and **258** through microwave irradiation at 175 °C in toluene, with and without MnO₂, led to no reaction observed in any experiment. To conclude, it is clear that the aromaticity is too high to break in annulation reactions. To develop the methodology further, an investigation

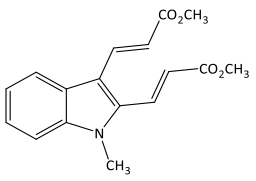
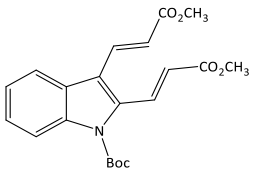
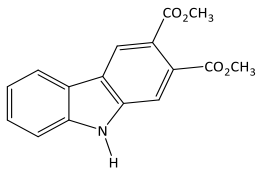
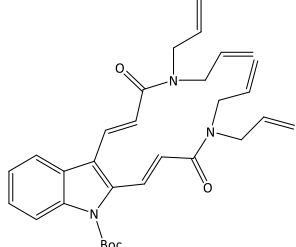
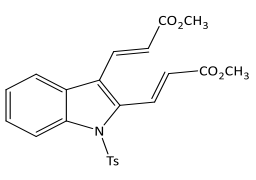
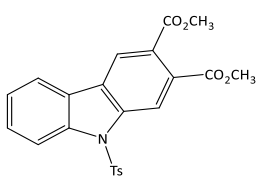
into the use of dimethyl-2,4,6-octatrienedioate **267** and dimethyl (2*E*,6*E*)-2,6-octadien-4-ynedioate **269** (Scheme **88**) as triene substrates to irradiate using microwave under the same conditions that mentioned above with or without MnO₂ to accelerate the oxidation.

All attempts to accomplish the desired products by 6 π -electrocyclisation were unsuccessful. These attempts were useless for triene compounds containing six-membered ring such as benzene. To apply more reactive 'triene' compounds it is therefore necessary to use substrates with five-membered ring such as indoles (Table **12**, Scheme **91**).



Scheme 91: 6 π -Electrocyclisation reaction of synthesised 'trienes' indoles

Table 12: 6 π -Electrocyclisation reaction of synthesised 'trienes' indoles

Entry	Triene	Procedures	Cyclised products	Yield%
1	 267	A	--	0
2	 268	<hr/> A <hr/> B	 275	<hr/> 0 <hr/> 69
3	 269	A	--	0
4	 271	<hr/> A <hr/> C <hr/> D	 276	<hr/> 0 <hr/> 0 <hr/> 71

A) Photochemical electrocyclisation in a Microwave: 15-30 min, toluene, 200 °C; **B)** Thermal electrocyclisation: 10% Pd/C (1.4 equiv.), bromobenzene, reflux, 15 h; **C)** Thermal electrocyclisation: 10% Pd/C (1.88 equiv.), dry xylene, reflux, overnight; **D)** DDQ (2 equiv.), bromobenzene, reflux, 3 h.

As can be seen from the data in Table 12 above and Scheme 91 that the microwave protocol tolerated **267**, **268**, **269** and **271** bearing the *N*-Me, *N*-Boc and *N*-Ts groups respectively, producing negative results using photochemical promotion at 175 °C in toluene. However, at thermal promotion it was revealed that the presence of protective groups of indole would be not

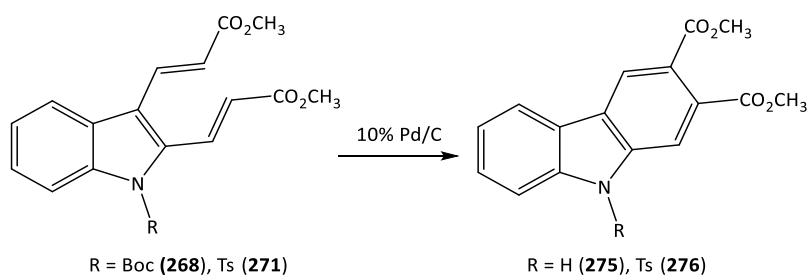
problematic. For successful completion of the synthesis of **275** bearing a Boc group at indole-1-*N* derived from **268** by catalytic reaction was subjected to 6π -electrocyclisation with 10% palladium on carbon in bromobenzene under reflux to give **275** in 69% yield. Interestingly, it was noticed that deprotection of the Boc group in **268** occurred. In addition to the synthesis of **276**, it was successfully prepared thermally only using DDQ in bromobenzene in a yield 71%, whereas no reaction was obtained by using 10% palladium on carbon. The NMR analysis confirmed the structure of **275** and **276**. Spectroscopic analysis by ^1H -NMR showed the disappearance of doublet protons of $-\text{CH}=\underline{\text{CH}}-$ (**a**, **c** positions) as shown in Scheme **91**.⁽¹³⁵⁾ However, given the failure of the indole triene to cyclise under TOP conditions, or in the presence of a compliant oxidant such as MnO_2 , it was realised that there was no benefit to further studies. The difficulty in preparing indole trienes with appended allyl esters or amides also meant that the 6π -electrocyclisation/Diels-Alder reaction could not be studied.

2.7 Conclusion:

- A one pot oxidation-Wittig sequence of 1,2-diols have been investigated as a route to α,β -saturated esters, where these diols were oxidised with MnO_2 and reacted with stabilised Wittig ylides. After several attempts for the synthesis of trienes was achieved to give 19-51% yield of products **267-269**, and **271**.
- Microwave-assisted one-pot synthesis of 'triene' substrate (**256**) failed to yield the corresponding product. This result is likely due to the high

energy barrier of breaking aromaticity of the benzene ring being unsurmountable.

- Thermal 6π -electrocyclisation of 'trienes' **268** and **271** with 10% Pd/C led to the preparation the requisite products in good to moderate yields.



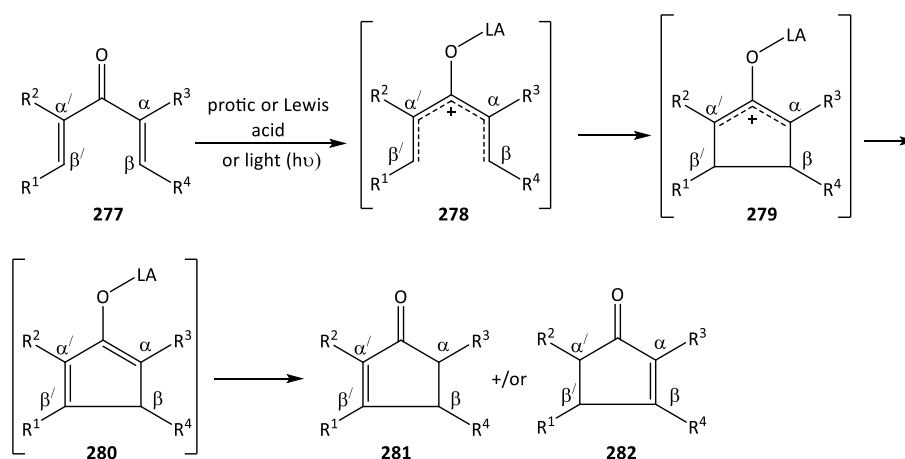
Chapter 3 Results and discussion II: Nazarov Cyclisation

3 Introduction:

There is a growing body of literature highlighting the importance of the development of efficient techniques for the construction of five-membered rings, particularly because they are abundant in natural product skeletons. The Nazarov reaction has been an object of research since the 1940s,^(48a) and is an important reaction for the preparation of cyclopentenones. It is based on the use of conjugated dienones which can be promoted with Lewis or Brønsted acids, *via* 4 π -electrocyclisation, to construct cyclopentenones.

3.1 Classical Nazarov cyclisation

The classical Nazarov reaction can be described as proceeding *via* the sequence of steps summarised in Scheme 92. Typically, a divinyl ketone **277** is treated with a strong Lewis or protic acid to form an intermediate (pentadienyl cation), followed by thermally 4 π -conrotatory cyclisation to generate an allylic carbocation. Loss of a proton leads to either cyclopentenone **281** or **282**. Generally, this reaction requires either a protic acid (CH₃SO₃H and CF₃SO₃H) or strong Lewis acid such as boron trifluoride ethyl etherate (BF₃·OEt₂), tin(IV) chloride (SnCl₄), titanium(IV) chloride (TiCl₄), or aluminum chloride (AlCl₃). More recently, more contemporary Lewis acids have been employed to promote Nazarov reaction, such as TMSOTf,⁽¹³⁶⁾ Cu(OTf)₂,⁽¹³⁷⁾ and PdCl₂(MeCN).^(138, 139)

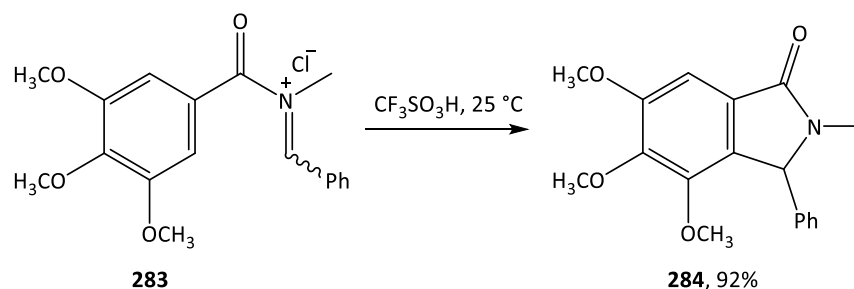


Scheme 92: The Classical Nazarov cyclisation of divinyl ketones **277**

3.2 Catalysis of Nazarov cyclisation

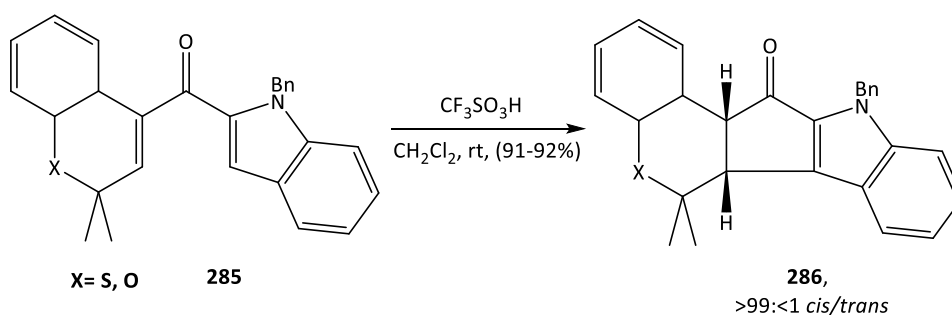
The catalysts for the Nazarov cyclisation can be grouped into the following types: Brønsted acids, organo-catalysts, heterogeneous catalysts, and Lewis acids including transition-metal catalysts.

It is common knowledge that Brønsted acids are among the most effectively used types of catalysts. Several types of Brønsted acids have been demonstrated in this chapter as examples namely; triflic acid,⁽¹⁴⁰⁾ *p*-toluenesulfonic acid,⁽¹⁴¹⁾ and triflamide.⁽¹⁴²⁾ Herein, many reports have focused on the use of triflic acid in the Nazarov reaction where firstly Klumpp *et al*^(140a) investigated electrocycloislation of *N*-acyliminium salts **283** *via* aza-Nazarov cyclisation to form the product **284**. The main aim of this study is to examine the differences between superacids and weaker acids. It was found that transformations using the weaker acid catalyst (trifluoroacetic acid) were ineffective giving a disappointing yield (17%). whereas, the use of superacid triflic acid instead afforded an excellent 92% yield for the transformation product (Scheme **93**).



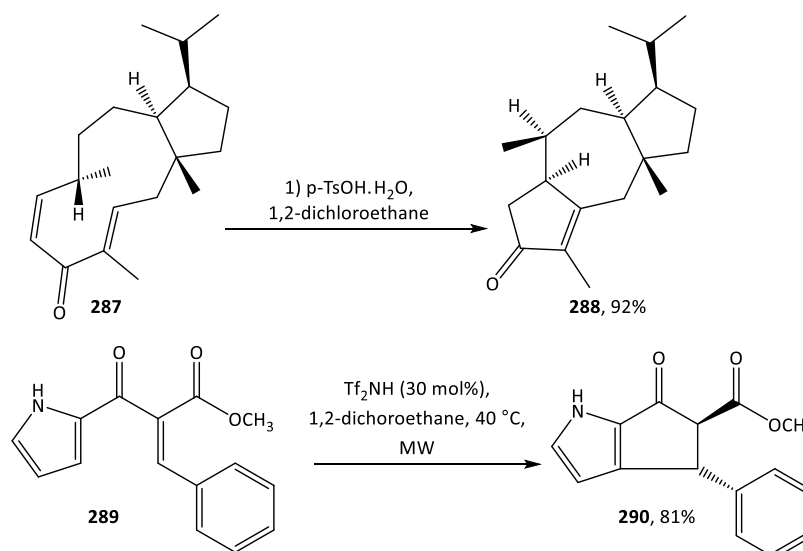
Scheme 93: Aza-Nazarov cyclisation of *N*-acyliminium salts **283** by triflic acid

In 2009, Panda *et al* reported a new and convenient synthetic procedure with an expansion of the Nazarov cyclisation to obtain fused aromatic or heteroaromatic tricycles **286** by reacting with different triflic catalysts to yield (91-92%) diastereoselectivity (>99:1 d.r.), as shown in Scheme 94.^(140b)



Scheme 94: The construction of tricycles **286** using Nazarov cyclisation

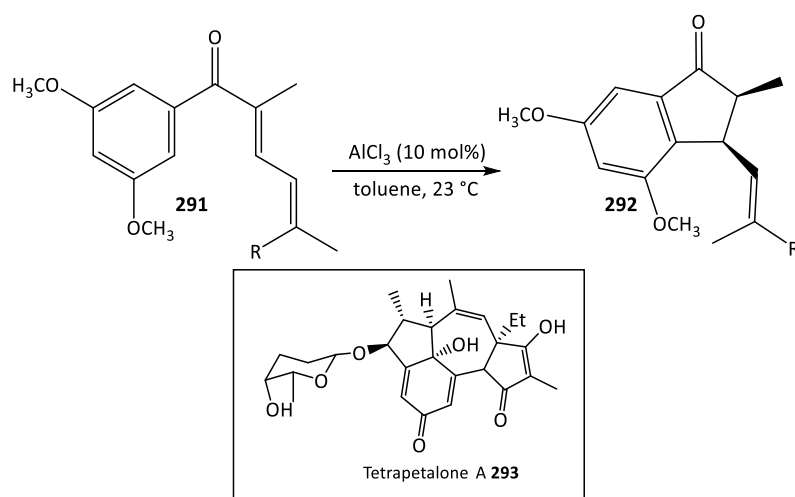
P-Toluenesulfonic acid (*P*-TsOH.H₂O) is one of the most important catalysts for the Nazarov reaction and has been extensively used under mild conditions for cyclisation of many Nazarov substrates.^(141a) Under TsOH-catalysed Nazarov conditions, the formation of product **288** from dolabelladienone **287** has been investigated by Williams and co-workers.^(141b) Furthermore, another significant catalyst used as a Brønsted acid catalyst, is triflimide where the dienone **289** can be cyclised *via* a microwave-assisted triflimide-Nazarov reaction affording 81% for the final product **290** (Scheme 95).⁽¹⁴²⁾



Scheme 95: catalytic Brønsted acids *via* Nazarov cyclisation

A variety of Lewis acids were employed in Nazarov cyclisation to cyclise substituted dienones that afforded good yield and stereoselectivity of the final products such as copper (II) salts,⁽¹⁴³⁾ iridium,⁽¹⁴⁴⁾ gold,⁽¹⁴⁵⁾ and active vanadium⁽¹⁴⁶⁾ complexes.

The aluminium chloride AlCl₃ catalyst reported by Sarpong and Marcus in 2010 has proved extremely active for the Nazarov cyclisation of aryl vinyl intermediate **281** for the construction of tetrapetalone A **293** (Scheme **96**). They found no cyclisation occurred when R = H because there were no 1,3-allylic interactions with the methyl group at the γ-position of the C=O group.⁽¹⁴⁷⁾



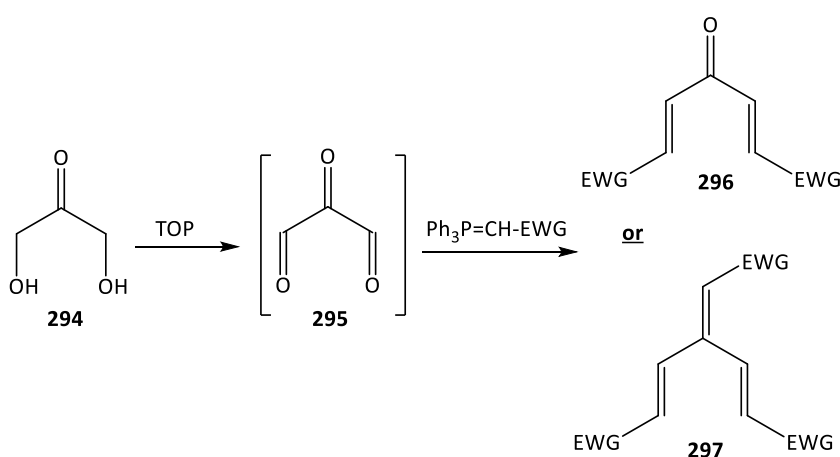
Scheme 96: Cyclisation of aryl vinyl intermediate **291** using an aluminium chloride catalyst

In the late 2000s, Itoh *et al* invested considerable effort into the use of iron salts as Nazarov catalysts, such as ferric chloride (FeCl_3), which work under mild conditions for the Nazarov cyclisation of polarised substituted thiophene enones.⁽¹⁴⁸⁾ However, other catalysts such as lithium perchlorate (LiClO_4) and scandium triflate $\text{Sc}(\text{OTf})_3$ ⁽¹⁴⁹⁾ gave no reaction with 2-substituted thiophene enones.

In other recent studies of transition metal-catalysed Nazarov cyclisation of indole enones, Qi-Lin and co-workers developed a method for cooperative catalysis by zinc dichloride (ZnCl_2) and chiral phosphoric acids (SPAs) to synthesise asymmetric products with excellent enantioselectivity. They noticed that the reaction of substrate with ZnCl_2 without SPA (co-catalyst) was slower than if used together; where the presence of SPA accelerated the reaction rate to afford the product in excellent yields at a range of temperatures.⁽¹⁵⁰⁾

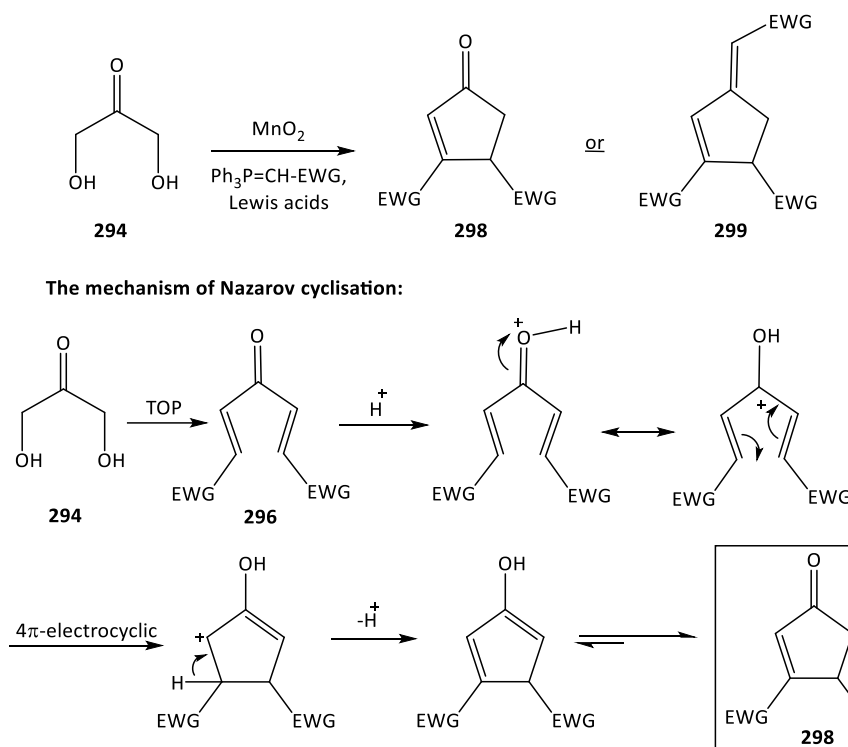
3.3 Project introduction:

The purpose of this work was to prepare dienes *in situ* from dihydroxyacetone **294** obtained *via* a TOP reaction. This work will pay attention to the possibility of preparation of trienes that can undergo vinylogous Nazarov reaction and will highlight the use of Lewis acid to promote the reaction. Dihydroxyacetone **294** will be used as a first example in this work to synthesise the desired compounds with illustrating the difficulties of this project (Scheme **97**).



Scheme 97: The hypothesised route for the construction of dienes and trienes

Additionally, Lewis acids-mediated TOP-Nazarov cyclisation reaction of dihydroxyacetone **294** has been applied for the synthesis of substituted cyclopentenones **298** or **299** through C–C bond formation in a one-pot procedure (Scheme **98**).



Scheme 98: Mechanism of the Nazarov cyclisation of **296**

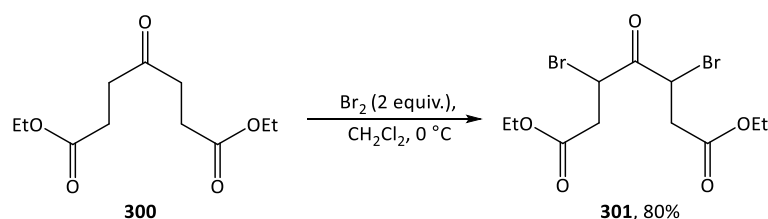
These above aims raise the following core project objectives:

- To avoid handling reactive/sensitive intermediates that could potentially support to a reduction in the production of by-product waste, the amount of solvent waste and the production costs.
- To examine conditions necessary to make dienes and trienes and investigate if we can control this reaction.
- To examine conditions to make Nazarov cyclisation as a final step.

3.4 Studies towards the construction of the divinyl ketone core from 4-oxopimelate

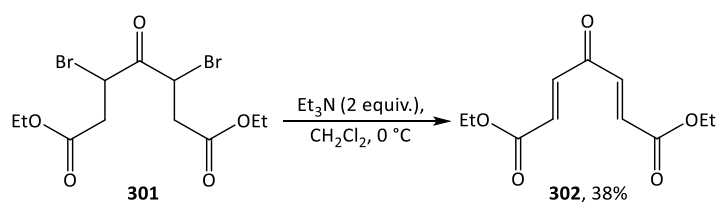
An insignificant amount of literature has been published on the formation of divinyl ketone of 4-oxopimelate⁽¹⁵¹⁾ and also cross-conjugated trienes.⁽¹⁵²⁾ Most researchers have used a single approach based on the Lemaire-Audoire and

Vogel method.⁽¹⁵³⁾ Vogel (1999) reports the formation of the diethyl (*E,E*)-4-oxohepta-2,5-diene-1,7-dioate **302** *via* two steps. Firstly, a selective dibromination of 4-oxopimelate **300** through the enol was done using bromine (Br_2) in dichloromethane at 0 °C to afford the desired diethyl-3,5-dibromo-4-oxoheptadioate **301** in 80% yield, as shown in Scheme 99. NMR analysis of **301** shows the appearance of triplet peak at 5.35 ppm (t, $J = 5.6$ Hz, 1H) that belongs to $-\text{CHBr}$, where the $-\text{CH}_2\text{CO}_2\text{Et}$ group was observed as a 2H multiple at 3.00-3.04 ppm and 3.25-3.32 ppm in the ^1H -NMR.

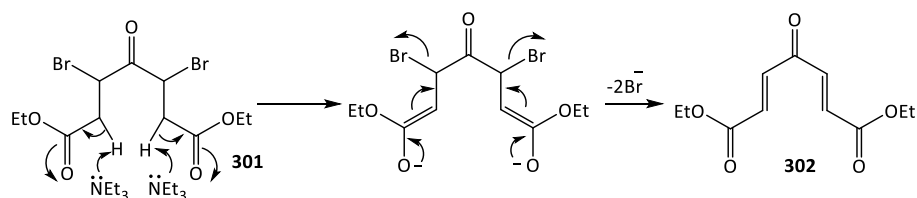


Scheme 99: The bromination of 4-oxopimelate **301**

Treatment of **301** with triethylamine led to the elimination of two molecules of hydrogen bromide (HBr) at 0 °C with the desired product **302** isolated in 38% yield as the second step and this reaction underwent the $\text{E}_{1\text{cb}}$ elimination, as can be seen from the Scheme 100. Spectroscopic analysis confirmed two protons with a 2,3-double bond pattern on the divinyl ketone, i.e. doublets at 6.81 and 7.23 ppm ($J = 15.9$ Hz, 2H). Preparation of **302** allowed investigation of TOP conditions to be surveyed by NMR and as a substrate to investigate triene formation.



The mechanism:



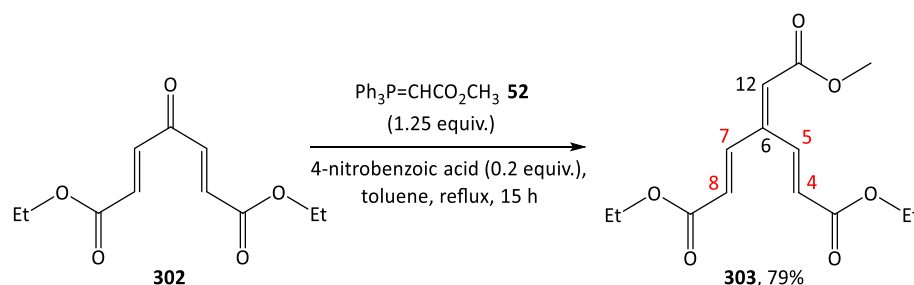
Scheme 100: The elimination reaction of **302** with its mechanism

Preparation of diethyl (*E,E*)-4-oxohepta-2,5-diene-1,7-dioate **302**, allowed us to attempt our next objective to prepare cross-conjugated trienes, followed by vinylogous Nazarov reaction.⁽¹⁵²⁾

3.5 Preparation of triene derivatives

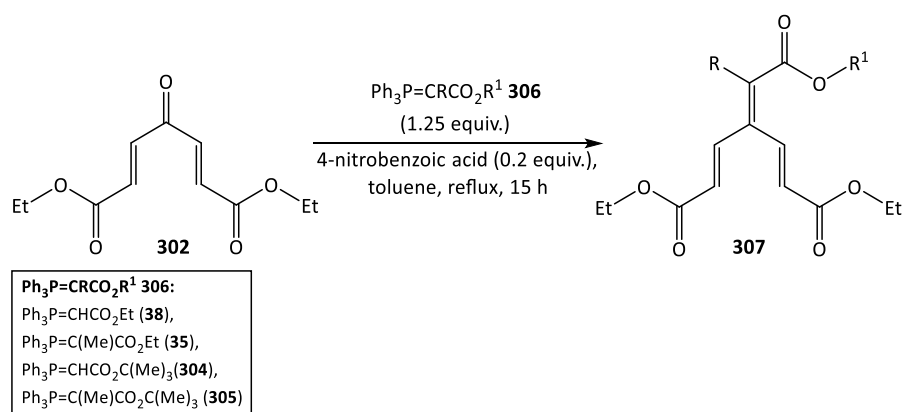
Having **302** compound, triene formation was undertaken with methyl (triphenylphosphoranylidene)acetate **52**. This ylide was chosen to provide a distinction NMR handle for analysis (i.e. the methyl ester). This reaction was performed by adding diethyl (*E,E*)-4-oxohepta-2,5-diene-1,7-dioate **302** and ylide **52** using 4-nitrobenzoic acid as a catalyst in toluene. After addition of ylide the mixture was refluxed and stirred for 15 h; this constituted a general procedure for all Wittig reactions attempted. When the reaction mixture was analysed by ¹H-NMR following evaporation *in vacuo* a mixture of divinyl ketone **302**, diethyl (*E,E*)-4-methylacrylate-2,5-diene-1,7-dioate **303** (product), ylide **52** and catalyst was observed in the crude mixture. Following chromatographic separation on silica gel, the spectroscopy analysis of **303** was confirmed by ¹H-NMR where the singlet protons at 3.73 ppm (s, 3H) indicate to methyl group (-

CH₃) in 79% yield. The proton of the alkene was observed at 6.16 ppm (12-H), whereas for the other four protons appear at 6.27 ppm (2H, **4-H**, **8-H**), 7.42 ppm (1H, **5-H**), and 8.28 ppm (1H, **7-H**) respectively (Scheme **101**).



Scheme 101: The Wittig reaction of divinyl ketone **302** using Lewis acid

To examine the steric effects of this definition, the scope was investigated with various ylides. Using the same method, other substrates have been successfully synthesised under the same conditions (toluene, reflux, 15 h). Four commercially available phosphorane ylides featuring electron withdrawing substituents: ethyl (triphenylphosphoranylidene)acetate **38**, (carbethoxyethylidene)triphenylphosphorane **35**, (*tert*-butoxycarbonylmethylene)triphenylphosphorane **304**, and *tert*-butyl 2-(triphenylphosphoranylidene)propionate **305**, were selected. The transformations were determined by examining the ¹H-NMR spectra of the products Scheme **102** and Table **13**.



Scheme 102: Preparation of triene derivatives

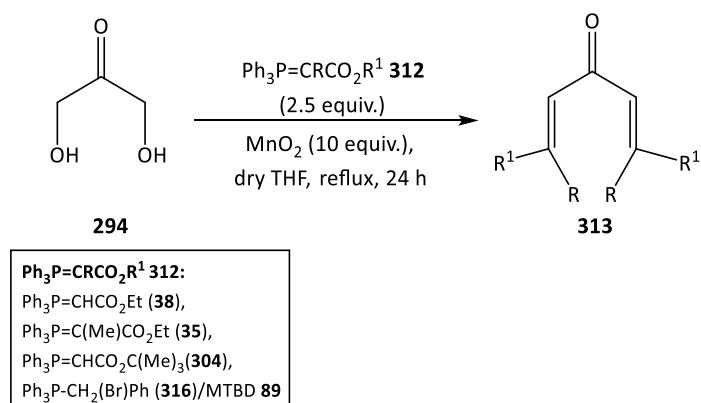
Table 13: Preparation of triene derivatives

Entry	Phosphoranes [306]	Products [307]	Yield %
1	Ph ₃ P=CHCO ₂ Et 38	 308	43
2	Ph ₃ P=C(Me)CO ₂ Et 35	 309	95
3	Ph ₃ P=CHCO ₂ CMe ₃ 304	 310	34
4	Ph ₃ P=C(Me)CO ₂ CMe ₃ 305	 311	47

It was gratifying to observe that these reactions had proved successful by analysing them by ^1H -NMR. The results in general showed the yields to be moderate but there was no significant steric effect given the similar results for **308-311**.

Following optimisation of the Wittig reaction of **294**, the TOP reaction was investigated (Scheme **103**, Table **14**) with four alternative ylides. Unfortunately, under standard TOP conditions, no reaction occurred when dihydroxyacetone **294**, phosphorane ylides **306** and 4-nitrobenzoic acid were reacted together in dry THF.

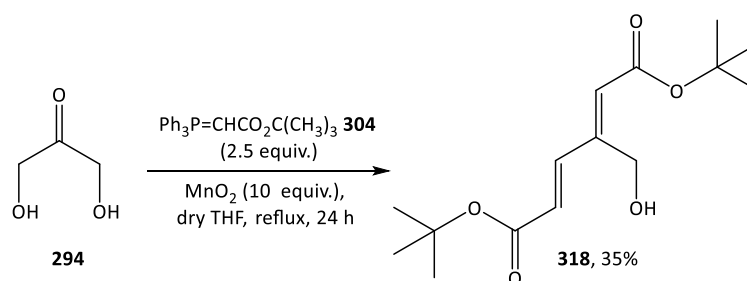
The synthesis of **302**, NMR analysis of the reaction mixture demonstrated that dihydroxyacetone **294** had transformed to product **302** in 15% yield; thus, the remaining alcohol **294** and ylide **38** were recovered unchanged from the reaction mixture in high recoveries (Scheme **103**). In addition, the use of the phosphorane ylide **35** in TOP reaction was therefore examined. Treatment of **294** with phosphorane **35** proceed to afford **314** in 20%; while a significant amount of **294** and ylide **35** remained. NMR analysis of the crude reaction mixture showed that proton peaks were observed at 1.43 ppm (t, $J = 6.4$ Hz) and 4.28 ppm (q, $J = 6.3$ Hz) indicate the ester group ($\text{CH}_3\text{CH}_2\text{O}-$), whereas, protons at 2.28 ppm (s), 7.20 ppm (s) are related to methyl and alkene groups respectively.

**Scheme 103:** Preparation of divinyl ketone derivatives using TOP reaction**Table 14:** Preparation of divinyl ketone derivatives using TOP reaction

Entry	Phosphoranes [312]	Divinyl ketone derivatives [313]	Yield%
1	Ph ₃ P=CHCO ₂ Et 38	<p style="text-align: center;">302</p>	15 (<i>E,E,E,Z</i>) (100:0)
2	Ph ₃ P=C(Me)CO ₂ Et 35	<p style="text-align: center;">314</p>	20 (<i>E,E,E,Z</i>) (0:0)
3	Ph ₃ P=CHCO ₂ CMe ₃ 304	<p style="text-align: center;">315</p>	NR
4	Ph ₃ P-CH ₂ (Br)Ph 316 /MTBD 89	<p style="text-align: center;">317</p>	NR

The reactions with alternative ylides **304** and **316** both proved to be unsuccessful. The crude reaction mixture showed in both cases that

decomposition had occurred. It is somewhat surprising that unexpected product **318** was obtained from the TOP reaction of **294** (Table 14, Entry 3) with ylide **304** in dry THF. The key to this unexpected transformation was considered to be the olefination step of carbonyl group (C=O) had occurred firstly instead of at the alcohol (Scheme 104) and analysis by ^{13}C -NMR confirmed that no ketone functionality was present. NMR analysis on this material showed the appearance of the signals due to the ($-\underline{\text{CH}_2}\text{OH}$) at 4.42 ppm, and hydroxyl group at 1.83 ppm (br.s).



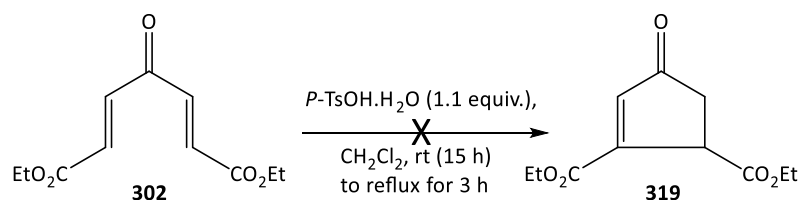
Scheme 104: The unexpected product **318** of TOP reaction

3.6 Synthesis of cyclopentenone derivatives

After the synthesis of divinyl ketones using both Wittig and TOP reactions, the next step is the construction of the cyclopentenone ring *via* Nazarov cyclisation. Hence, the precursors **302**, **308**, and **311** were reacted with a variety of Lewis or Brønsted acids, either at room temperature or under reflux conditions.

With the aim to cyclise firstly divinyl ketone **302**, treatment of **302** with 1.1 equiv. of $p\text{-TsOH}\cdot\text{H}_2\text{O}$ in dichloromethane was selected, either at ambient temperature or under reflux. There was no evidence that $p\text{-TsOH}\cdot\text{H}_2\text{O}$ catalyst has any influence on the Nazarov cyclisation of **302**; divinyl ketone **302** have

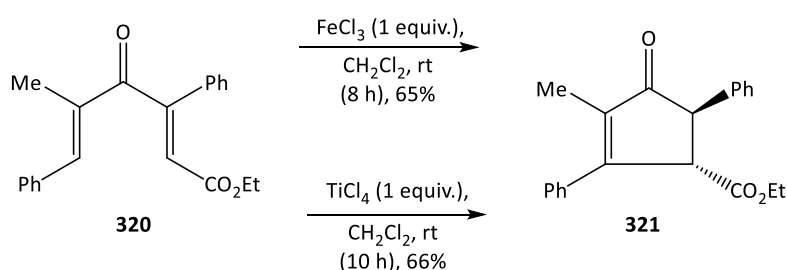
totally recovered unchanged in the reaction mixture (Scheme 105). It found that there was no solvent effect on this reaction; changing from dichloromethane to acetonitrile had no effect on the Nazarov reaction rate.



Scheme 105: The Nazarov cyclisation of **302** using $p\text{-TsOH}\cdot\text{H}_2\text{O}$ catalyst

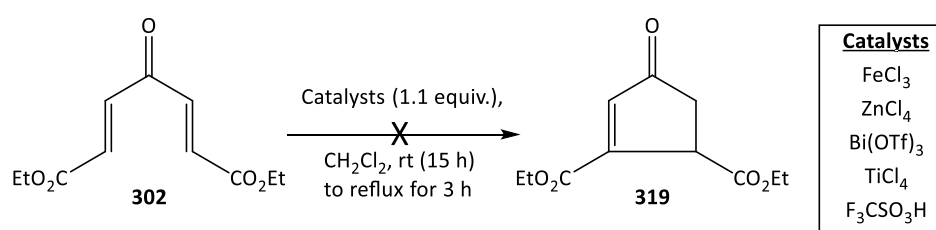
Due to the failure of using $p\text{-TsOH}\cdot\text{H}_2\text{O}$ catalyst, several Lewis acids namely zinc chloride (ZnCl_2), titanium(IV) chloride (TiCl_4) and bismuth(III) triflate ($\text{Bi}(\text{OTf})_3$) were screened. These attempted cyclisations with those catalysts in dichloromethane failed to deliver any products.

The Nazarov cyclisation was not observed; either at ambient temperature or under reflux. The successful preparation of cyclopentenones **321** from divinyl ketone **320** has been achieved frequently by use of FeCl_3 and TiCl_4 catalysts by Sudhakar *et al*, as shown in Scheme 106.⁽¹⁵⁴⁾ When the reaction was run for 15 h at room temperature to heat under reflux further 3 h there was no product obtained due to decomposition of **302**



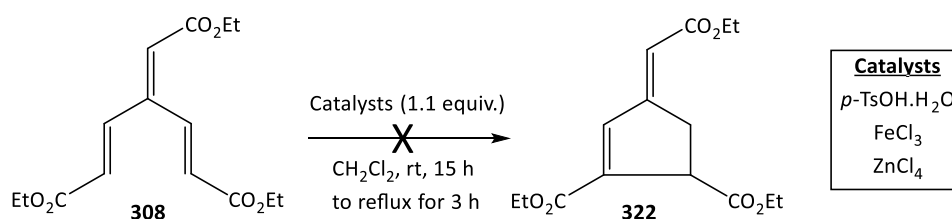
Scheme 106: The successful cyclisation of divinyl ketone **320**

Initially all these catalysts were tested; however, since it proved impossible to recognise the cyclopentenone products in any of the spectra of the crude reaction, the use of Brønsted acids as catalysts was considered. Herein, triflic acid ($\text{F}_3\text{CSO}_3\text{H}$) was examined with divinyl ketone **302** under the same conditions previously mentioned (Scheme 107). Unfortunately, no cyclisation was observed and NMR analysis confirmed just the presence of peaks that related to starting material **302** (Scheme 107). However, Shindo *et al* (2007) carried out a number of investigations into the successful Nazarov cyclisation. When treated with $\text{F}_3\text{CSO}_3\text{H}$, divinyl ketones were successfully converted into cyclic products in 39% yield.⁽¹⁵⁵⁾



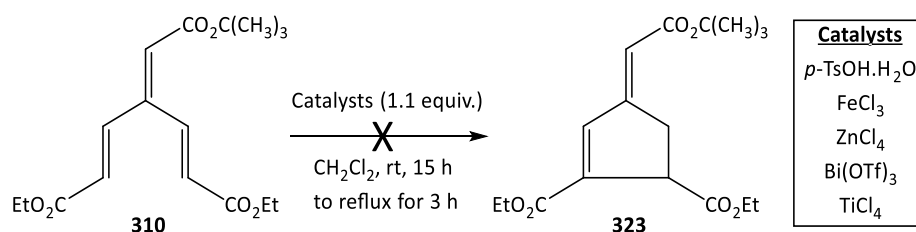
Scheme 107: The Nazarov cyclisation of **302** using Lewis acids

To confirm that such catalysts are responsible for the control of the reaction performance, a reaction of **308** with three Lewis acids was investigated namely $p\text{-TsOH}\cdot\text{H}_2\text{O}$, ZnCl_4 , and FeCl_3 . The results obtained from this set of experiments using these catalysts were eventually disappointing. They showed that no cyclopentenones were obtained and only the starting material **308** could be noticed *via* NMR analysis of the crude mixture (Scheme 108).



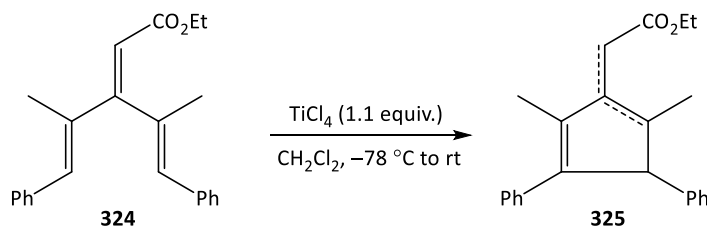
Scheme 108: The Nazarov cyclisation of **308** using Lewis acids

The preparation of desired cyclopentenone **323** proved more troublesome using substrate **310**. Many procedures have been employed for the synthesis of **323** from the reaction of **310** with five catalysts including, $p\text{-TsOH}\cdot\text{H}_2\text{O}$, FeCl_3 , ZnCl_4 , $\text{Bi}(\text{OTf})_3$, and TiCl_4 . No reaction was observed even after extended stirring or under reflux, as shown in Scheme 109.



Scheme 109: The attempted synthesis of cyclopentenone **323**

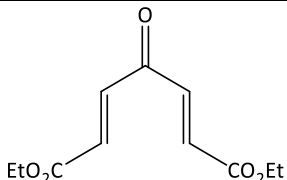
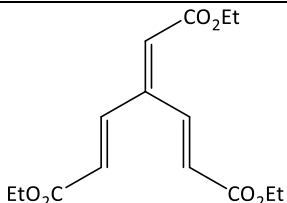
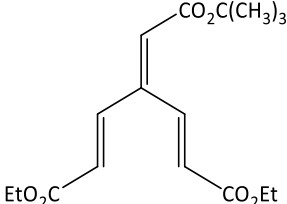
However, such substituted substrates have been successfully cyclised *via* a Nazarov cyclisation in particular using a TiCl_4 catalyst. When triene **324** was treated with Lewis acid (TiCl_4), a mixture of cyclopentenone regioisomers was formed in 76% yield (Scheme 110).⁽¹⁵²⁾



Scheme 110: An example of the vinylogous Nazarov reaction

Table 15 illustrates the summary of TOP reactions with these three substituted trienes, from ambient to reflux conditions, for the formation of cyclopentenones (Schemes 105-107).

Table 15: Summary of the attempted synthesis of cyclopentenone derivatives

Entry	Divinylketones	Lewis acids	Conditions	Result
1*	 302	<p><i>p</i>-TsOH.H₂O</p> <p>FeCl₃</p> <p>ZnCl₄</p> <p>Bi(OTf)₃</p> <p>F₃CSO₃H</p> <p>TiCl₄</p>	<p>CH₂Cl₂, rt,</p> <p>15 h to</p> <p>reflux for</p> <p>3 h</p>	NR [#]
2	 308	<p><i>p</i>-TsOH.H₂O</p> <p>FeCl₃</p> <p>ZnCl₄</p>	<p>CH₂Cl₂, rt,</p> <p>15 h to</p> <p>reflux for</p> <p>3 h</p>	NR
3	 310	<p><i>p</i>-TsOH.H₂O</p> <p>FeCl₃</p> <p>ZnCl₄</p> <p>Bi(OTf)₃</p> <p>TiCl₄</p>	<p>CH₂Cl₂, rt,</p> <p>15 h to</p> <p>reflux for</p> <p>3 h</p>	NR

*This reaction was done also under room temperature to reflux conditions in acetonitrile. [#] NR indicates no reaction occurred

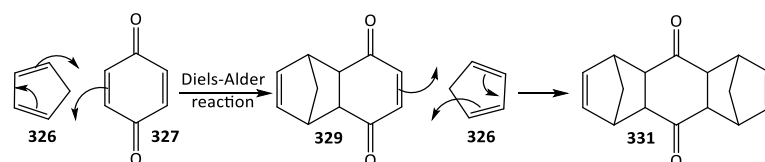
To summarise, the results of vinylogous Nazarov reaction were disappointing. ¹H-NMR analysis of the crude mixtures revealed that no cyclisation of the trienes had occurred even under ambient conditions. Most of the reactions showed only that the starting material was been unchanged; unfortunately, no tractable product could be observed by TLC or NMR spectroscopy and the starting material completely decomposed in particular entry 1 (Table 15) when FeCl₃ as a catalyst was used with the substrate 302.

4 Conclusion:

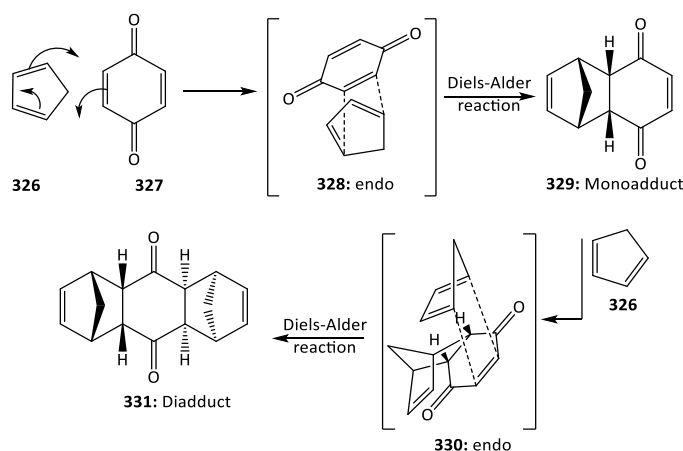
- Using modified TOP reaction consisting of dihydroxyacetone **294** with a variety of phosphorane ylides in toluene at reflux; a successful olefination workup process was set up for the construction of trienes.
- Three substrates have been employed to investigate *via* Nazarov reaction mediated by a variety of Lewis and Brønsted acids. Though in all attempts to cyclise synthesised trienes, this method does not form substituted cyclopentanones.

Chapter 4 Results and Discussion III: Diels-Alder Reaction**5 Introduction:**

In the history of organic chemistry, the Diels-Alder reaction is one of the most important and innovative strategies developed for the synthesis of target molecules.⁽¹⁵⁶⁾ The Diels-Alder reaction is a [4+2]-cycloaddition reaction between a conjugated diene (4π) and a dienophile (2π) to produce a cyclohexene. The study of the reaction of cyclopentadiene **326** with quinone **327**, as shown in Scheme **111**, was first carried out by Otto Diels and his student, Kurt Alder (1928). The importance of the reaction and its utility led to the award in 1950 of the Nobel Prize for their achievements in developing the reaction.



Mechanism of the double Diels-Alder reaction:



Scheme 111: The discovery of the Diels-Alder reaction in 1928

The Diels-Alder reaction is favoured particularly for the rapid development of molecular complexity. Therefore, the use of the Diels-Alder reactions in a cascade process to generate multiple rings in tandem reactions is a very promising approach for the synthesis of important biological scaffolds.^(157, 158)

5.1 Dienes and Dienophiles

A variety of conjugated dienes and substituted dienophiles have been the subject of studies in the Diels-Alder reaction. It is apparent from the Figure 11 that various examples have been collected according to their types of chains and rings, where conjugated dienes basically comprise two double bonds. Two geometries of conjugated dienes are possible; *cisoid* 332 and *transoid* dienes 333. Such studies, however, have shown that the *transoid* diene is unreactive due to the *trans* arrangement, as shown in Figure 11. In a study which set out to determine the reactivity of dienes, Sauer (1967) found that cyclic dienes are more reactive than the open chains. Additionally, the electronic impact of substituents in the diene have a significant effect on the rate of Diels-Alder reaction.⁽¹⁵⁹⁾ Generally, the presence of electron donating groups in dienes accelerate the reaction, as do electron withdrawing groups in dienophiles. However, dienophiles bearing electron donating substituents accelerate the reaction with electron withdrawing substituents in dienes, and this term called “*inverse electron-demand Diels-Alder reaction*” (IED-DA).

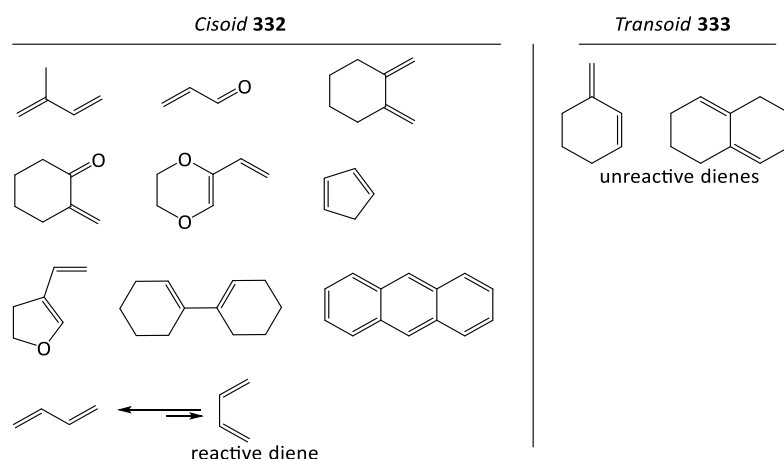


Figure 11: Examples of reactive and unreactive conjugated dienes

In terms of dienophiles, electron withdrawing groups, a weak π -bond, and the release of ring strain increase the reactivity of dienophiles. Some examples of dienophile are shown in Figure 12. It is well-known that ethene (C_2H_4), the simplest dienophile, is a poorly reactive dienophile in Diels-alder reactions.⁽¹⁶⁰⁾

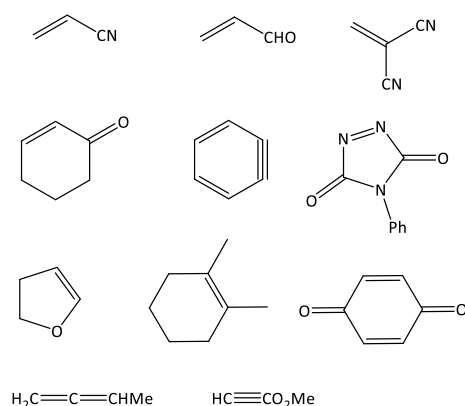


Figure 12: Examples of common dienophiles

5.2 Mechanistic aspects

Mechanistic aspects have been the subject of many classic studies in Diels-Alder reactions; typically, there are many combinations of carbon and hetero fragments that lead to formation of cyclic ring systems. This variety of combinations illustrates the massive versatility of the Diels-Alder reaction.⁽¹⁶¹⁾

There are two major classes of Diels-Alder reactions in terms of their electronics, one is the inverse electron demand addition and the other is normal electron demand addition. This classification depends on the rate of reaction in the presence of substituents (electron withdrawing and electron donating groups). The presence of electron withdrawing groups on the diene and electron donating ones on the dienophile lead to accelerate inverse electron demand reactions, while the opposite of these substituents promotes the normal electron demand cycloadditions. The effect of these substituents on the rate of reaction can be understood through the Frontier Molecular Orbital (FMO) theory, which was formulated by Woodward and Hoffmann,⁽¹⁶²⁾ Fukui⁽¹⁶³⁾ and later Houk amongst others.⁽¹⁶⁴⁾ As can be seen in Figure **13**, the interaction between the HOMO and LUMO for both the dienophile and diene is central to the efficacy of Diels-Alder reactions. In terms of the Woodward and Hoffmann rules, the construction of new σ -bonds leads to the conservation of the orbital symmetry. Consequently, there are no intermediates formed in these pericyclic Diels-Alder reactions.

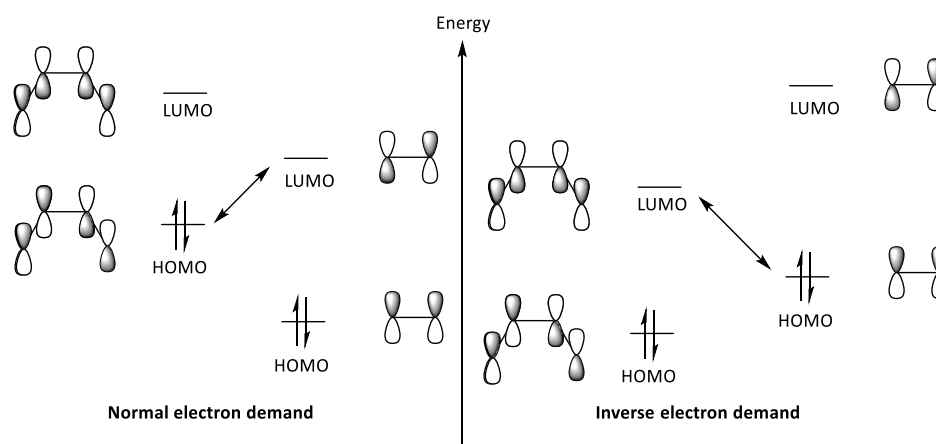


Figure 13: The FMO theory of inverse and normal electron demand reactions

According to the *endo* and *exo* modes, it has been proposed that secondary orbital interactions play an important role in Diels-Alder reaction (Figure 14), shows such interactions between cyclopentadiene and methyl vinyl ketone. In a study conducted by Woodward and Katz (1958),⁽¹⁶⁵⁾ it was shown that the possibility of overlap between π -orbitals of the carbonyl group of the dienophile and the HOMO-diene in the *endo* mode is symmetrically allowed. Hence, the stabilisation of the *endo* intermediate led to formation of the *endo* product faster than formation of the *exo* adduct. Indeed, few studies of Diels-Alder reactions in the literature show that the *exo* adduct is the main product.⁽¹⁶⁶⁾ The more surprising aspect is the *endo* selectivity of some reactions of dienophiles that bear substituents with no π -orbitals leading to form secondary orbital interactions as well.⁽¹⁶⁷⁾

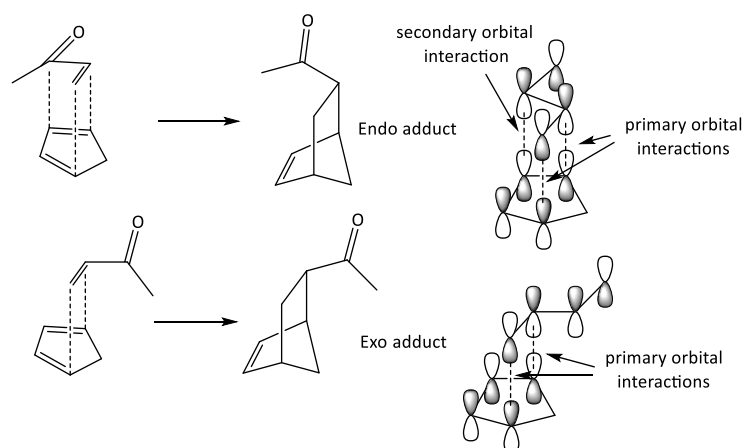


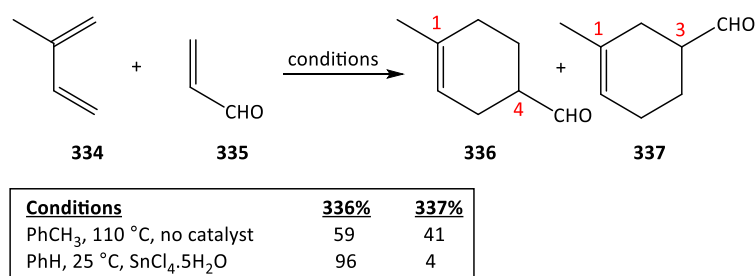
Figure 14: The explanation of Endo and exo modes of the Diels-Alder reaction of cyclopentadiene with methyl vinyl ketone

5.3 Regiochemistry and Stereochemistry

Many researchers have invested considerable effort into understanding the mechanism for the formation of adducts depending on the orientation of diene and dienophile substituents, and on the reaction conditions. This has become an area of increasing interest, with regiochemistry and stereochemistry being important considerations.

Typically, two isomeric adducts form based on the orientation of groups in these adducts *via* the reaction between an unsymmetrical diene and dienophile. Also, the regiochemistry of the adduct depends on the nature and number of substituents on both reactants. In the literature on regiochemistry, the relative importance of multi substituents on dienophile and diene has been subject to considerable discussion. Consequently, the presence of two different groups on the diene means one of them will be the regiodirector leading to control of the reaction, depending on the electronic effects of substituents. For example, the reaction of acrylic acid derivatives with 1- or 2-substituted butadienes gives rise to afford 1,3- or 1,4- adducts respectively,

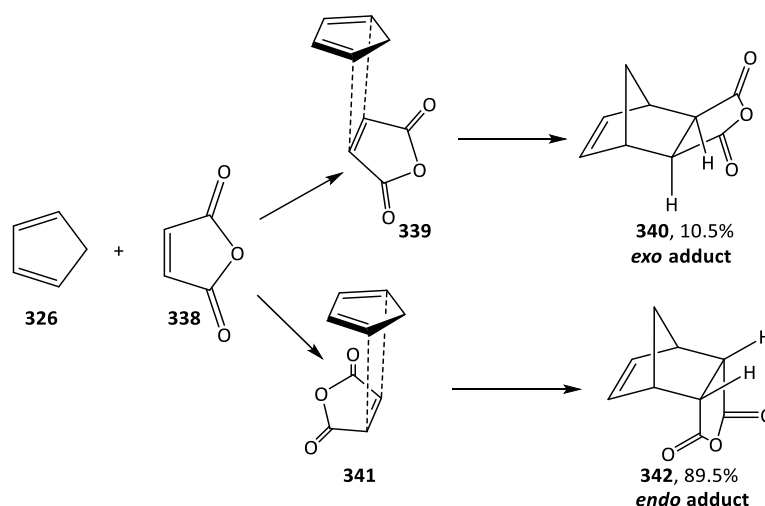
however, one adduct often forms in excess in the presence of Lewis acid. For example, the reaction of acrolein **334** with isoprene **335** as illustrated in Scheme **112**, it was noticed that the proportion of the 1,4-adduct **336** increases in the presence of SnCl_4 compared with other adduct **337**.⁽¹⁶⁸⁾



Scheme 112: The effect of Lewis acid in Diels-Alder reaction

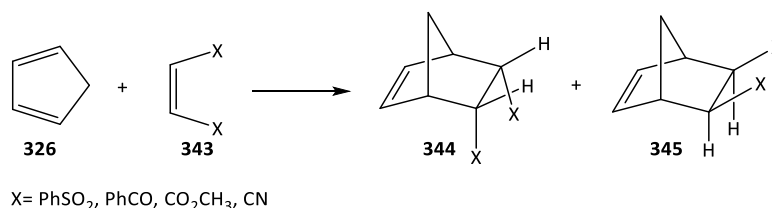
Two empirical rules can be applied to predict the stereochemistry of the adduct namely the (*cis*) principle and the *endo* rule. The (*cis*) principle was firstly recognised by Alder and Stein (1937),⁽¹⁶⁹⁾ where the suitable explanation is that dienes in which the substituents (both groups either outside or inside) at the **C-1** and **C-4** positions occupy the same orientation in the *s-cis* configuration will give the *cis* product and this applies to dienophile as well.⁽¹⁷⁰⁾ In stark contrast, the *endo* rule depends on the arrangement of both diene and dienophiles in parallel planes that can be shown in the transition state. Generally, the formed 1:1 adducts are obtained by a reaction of *cis*- or *trans*-dienophiles react with dienes with its retention of the *cis* or *trans* arrangement of the substituents in the dienophile. These products can include new bicyclic structures. In the literature, the terms '*endo*' or '*exo*' tend to be used to refer to the orientation of the substituted groups on the dienophile with the diene

with respect to the diene. Scheme 113 illustrates that the reaction of cyclopentadiene **326** with maleic anhydride **338** almost affords the *endo* isomer **342** while thermodynamically the *exo* adduct **340** is more a stable compound.⁽¹⁵⁹⁾



Scheme 113: The Alder ‘*Endo*’ rule in Diels-Alder reaction

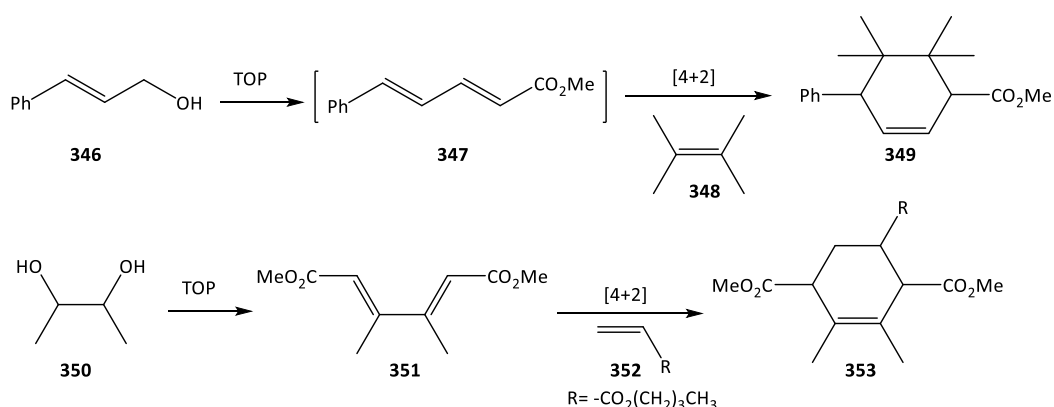
The addition of cyclic dienes to cyclic dienophiles follows the *endo* rule. In contrast, the reaction of 1,2-disubstituted alkenes with cyclic dienes undergoes Alder’s *endo* rule only. In particular, in the study of substituted maleic acid derivatives, when $X = \text{PhCO}$ or PhSO_2 the reactions afford *endo* product **344** without any noticeable amounts of *exo* product whereas, $X = \text{CO}_2\text{CH}_3$ or CN , the two adducts **344** and **345** are formed in an approximate ratio of 75:25 (Scheme 114).⁽¹⁷¹⁾



Scheme 114: The exemption of Alder’s *endo* rule

5.4 Project introduction:

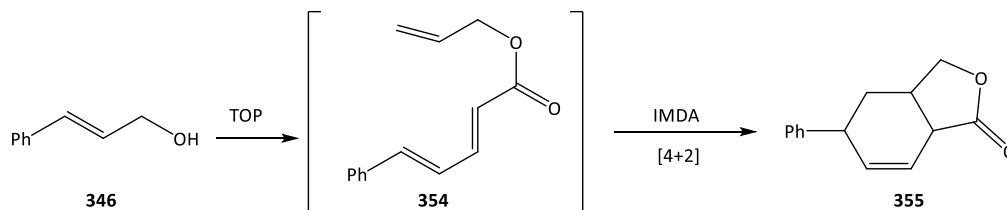
The purpose of this investigation is to explore the possibility of synthesising new substrates that could undergo a tandem sequence to make cyclic compounds. This strategy is based on a TOP-Diels-Alder sequence, for example, if cinnamyl alcohol **346** was treated with phosphorane ylide **52** under standard TOP conditions (MnO_2 in toluene/THF, reflux) and 2,3-dimethyl-2-butene **348**, it could conceivably react to give the adduct **349**. Another alternative substrate is 2,3-dihydroxy butane **350**, which could react with cinnamyl alcohol **346** to form the adduct **353**, as shown as in Scheme 115.



Scheme 115: The prospective TOP-Diels-Alder sequence

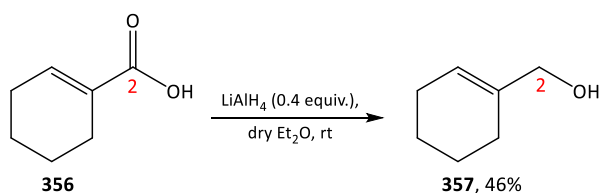
In this event, we examined the ability of alcohols **346** and **350** to undergo these diene forming reactions, followed by reacting with dienophile such as butyl acrylate to afford a final product. The choice of 2,3-dihydroxy butane derivatives was upon the basis of availability and stability of the diols; α,β -diketones are too unstable to undergo this sequence.

A third strategy, could be to introduce the intramolecular Diels-Alder tether of cinnamyl alcohol **346**, where two components are constrained in the same molecule and adduct is formed in a single step (Scheme **116**).



Scheme 116: The TOP-intramolecular Diels-Alder sequence of **346**

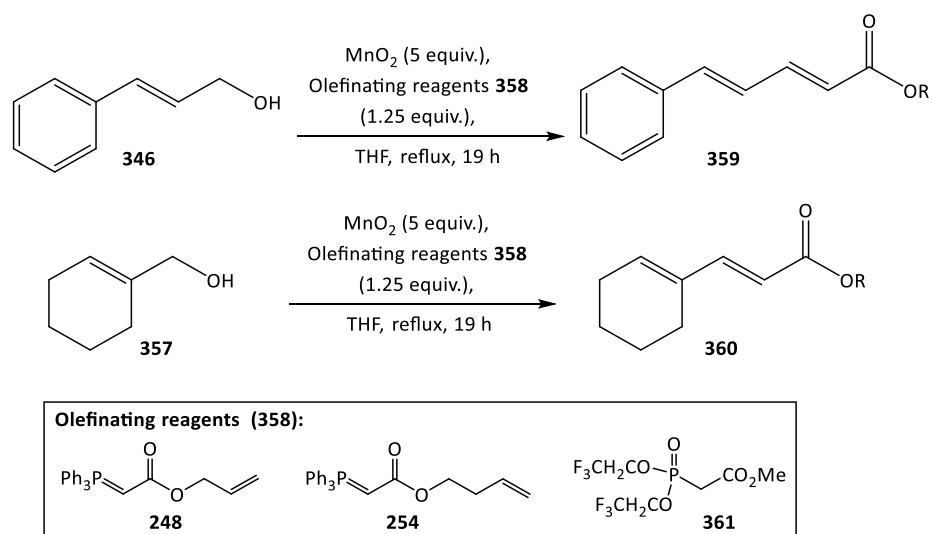
In an initial experiment, alcohol (cyclohexenmethanol) **357** was made from 1-cyclohexene-1-carboxylic acid **356** by reduction with LiAlH_4 in 46% yield (Scheme **117**). The IR spectrum showed absorbance characteristic of hydroxyl group at 3325 cm^{-1} .⁽¹⁷²⁾ The ^1H -NMR spectrum showed a singlet at 3.87 ppm which integrated for two protons, indicating a CH_2 group at the C-2 position. The proposed structure in the ^{13}C -NMR spectrum was proved by the appearance of the new methylene group at 67.5 ppm.



Scheme 117: The reduction reaction of 1-cyclohexene-1-carboxylic acid **356**

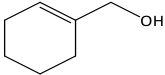
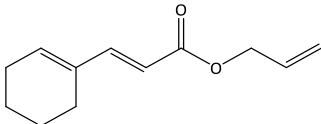
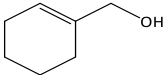
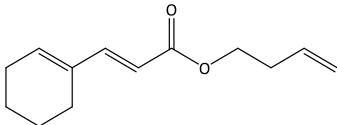
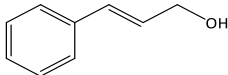
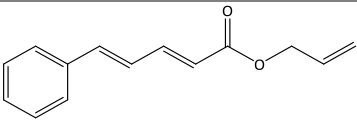
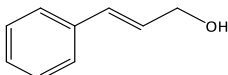
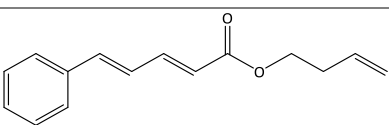
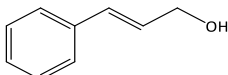
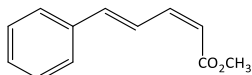
With alcohols **346** and **357** in hand, the formation of the diene derivatives *via* TOP reactions involved the reaction of alcohols **346** and **357**, phosphorane ylides **358** and MnO_2 in THF. Allyl-(triphenylphosphoranylidene) acetate **248**, 3'-butyen-1'-yl-2-(triphenylphosphoranylidene)acetate **254** and the readily

available bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate **361** ylides were used to test these reactions (Table 16, Scheme 118).



Scheme 118: TOP reaction of alcohols **346** and **357**

Table 16: TOP reaction of alcohols **346** and **357**

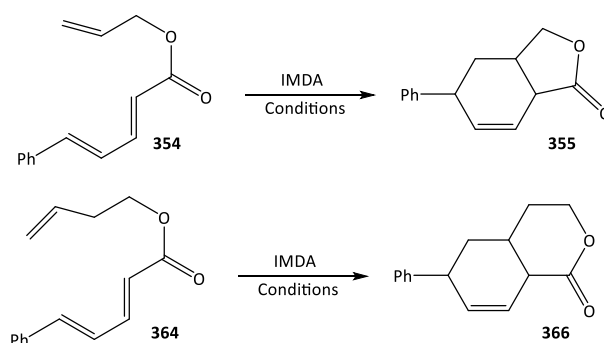
Entry	Alcohol	Ylide (358)	yield%
1	 357	248	 362, 13%
2	 357	254	 363, 11%
3	 346	248	 353, 32%
4	 346	254	 364, 31%
5	 346	361/ MTBD 89	 365, no reaction

The initial reaction (Entry **1**) with allyl ylide **248** appeared successful, with 13% yield of the product **362** observed. Furthermore, a large amount of unreacted cyclohexenemethanol **357** was present as well allyl ylide. Homo allyl ylide **254** was alternatively used for the synthesis of **363** (Entry **2**), where it was noticed that only 11% yield was afforded after purification using silica gel by column chromatography.

In terms of entries (3-5), the standard experiments above proved that the allyl and homo allyl ylides also reacted poorly with **346** and no reaction was observed with Still-Gennari reagent **361**. These findings are surprising but could be repeated.

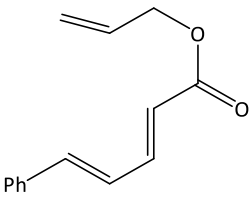
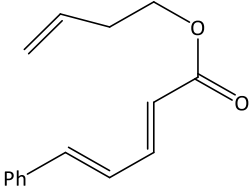
Following the TOP reaction, the IMDA reaction was examined using the tethered electron alkene. Unfortunately, with all attempts investigated using various Lewis catalysts failing to produce the desired adducts.

Thus, application of the attempted reaction to a range of catalysts, a variety of Lewis catalysts under thermal and ambient conditions illustrated in Scheme 119 and Table 17 were attempted.



Scheme 119: Attempts for the construction of Diels-Alder adducts **355** and **366**

Table 17: Attempts for the construction of Diels-Alder adducts **355** and **366**

Entry	Cinnamyl esters	Conditions/ overnight ^(a)	Result
1	 354	^b LiBF ₄ (1.0 M MeCN), dry benzene, rt	No reaction
2		^c Ph ₂ O, reflux	No reaction
3		^d Hydroquinone, xylene, reflux	No reaction
4		^d Hydroquinone, mesitylene, reflux	No reaction
5	 364	^e Bi(OTf) ₃ , toluene, reflux	Decomposed
6		^e <i>p</i> -TsOH. H ₂ O, toluene, reflux	Decomposed
7		^e F ₃ CSO ₃ H, toluene, reflux	Decomposed
8		^c Ph ₂ O, reflux	No reaction
9		^b LiBF ₄ (1.0 M MeCN), dry benzene, rt	No reaction

^(a)These reactions were performed using a slight modification of the method described in their literatures. ^(b)Reaction was carried out in 0.06 mmol of LiBF₄ solution with (**354**) and 0.053 mmol of LiBF₄ solution with (**364**).⁽¹⁷³⁾ ^(c)Reactions were carried out on (1 equiv.) scale in diphenyl ether. ^(d)Reaction was carried out in 2 mmol scale of hydroquinone.⁽¹⁷⁴⁾ ^(e)Reaction was carried out in 0.087 mmol scale.

Initial attempts at using LiBF₄ (1.0 M MeCN), resulted in no reaction occurring (Entries **1** and **9**), when **354** and **364** treated with LiBF₄ (1.0 M MeCN) in dry benzene overnight. Efforts to increase the possibility of promotion of IMDA reaction of **354** using five different catalysts were investigated further. The thermal IMDA reaction of both of **354** and **364** in diphenyl ether was investigated and resulted unchanged in the starting materials. Alternatively, treatment of **354** in the presence of the oxygen scavenger hydroquinone, in xylene was attempted. However, no adduct was observed, even when mesitylene was employed instead Hydroquinone is added to the reaction

mixture to inhibit the polymerisation of the participating dienes/ dienophile of the substrate in intramolecular Diels-Alder Reaction.⁽¹⁷⁴⁾

Due to the failure to make the desired products from the IMDA reaction of **354**, homo allyl ester **364** was instead investigated. It was hoped that the formation of a 6.6 fused bicyclic system would be energetically more favourable. Therefore, **364** was reacted with Lewis and Brønsted acids such as Bi(OTf)₃, *p*-TsOH.H₂O and F₃CSO₃H, but the formation of adduct **366** was unsuccessful due to the decomposition of **364**.

Therefore, the observed low reactivity in Lewis acid-catalysed IMDA reaction of cinnamyl esters could be probably attributed to the electronic demands of the ester group in the transition state (Figure 15). It was thought that conjugation of the carbonyl with the diene π -system reduces the electronic demand for overlap with the oxygen of the ester group in the transition state could be prevented cyclisation. This explanation is consistent with the literature.⁽¹⁷⁵⁾

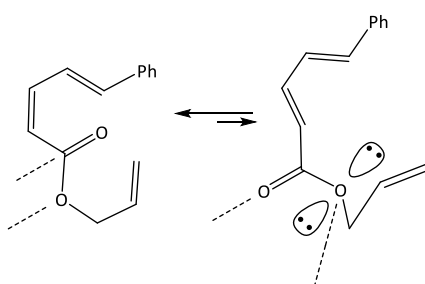


Figure 15: The electronic demand for overlap with the oxygen of the ester group

This observation is in agreement with Martin and co-workers (1983) findings which showed no cyclisation was observed for the isomer **367** (Figure 16).⁽¹⁷⁶⁾

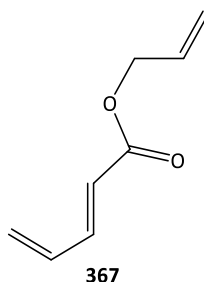


Figure 16: No cyclisation up to 275 °C

5.5 Synthesis of diols

Commercially available diols were employed to undergo TOP reaction, including 2,3-butanediol **350**, hydrobenzoin **368**, 1-phenyl-1,2-ethanediol **369**, and 1,2-cyclohexanediol **370**; whereas others were successfully prepared in the lab (Figure 17).

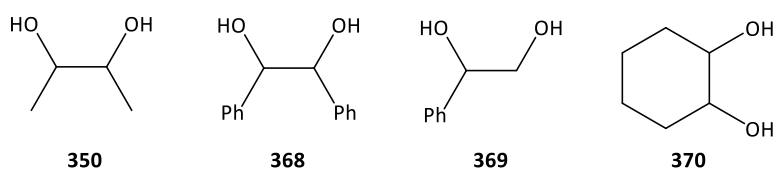
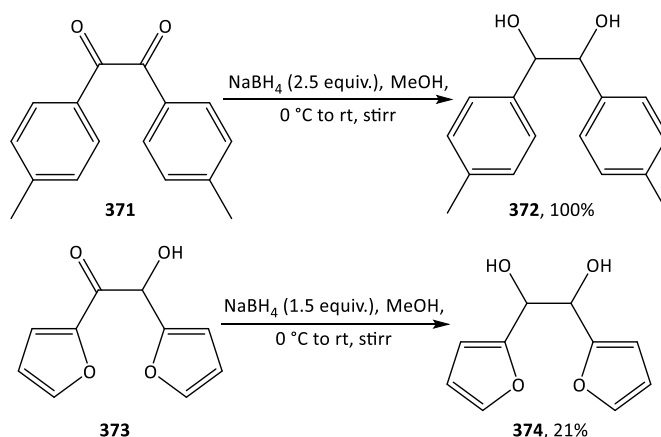


Figure 17: Four commercial diols used in this project

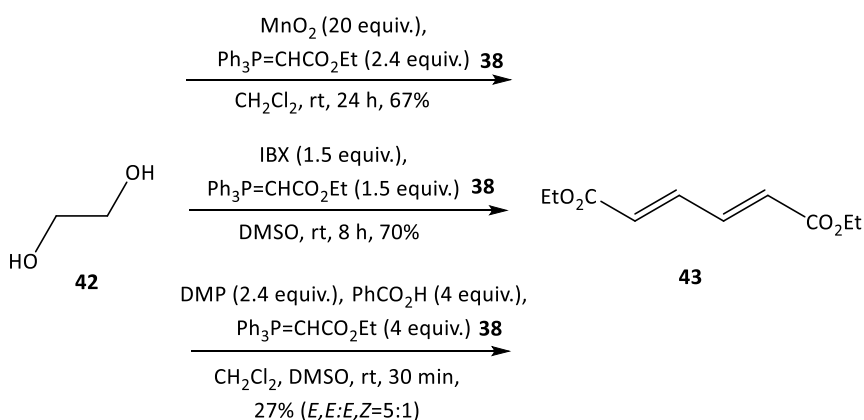
An improved procedure, published in 2008,⁽¹⁷⁷⁾ involved the use of a 4,4'-dimethylbenzil and also furoin as starting materials to be reacted with 2.5 equivalents of NaBH₄ to form 1,2-ditolylethane-1,2-diol **372**⁽¹⁷⁷⁾ and 1,2-difuran-2-yl-ethane-1,2-diol **374**⁽¹⁷⁸⁾ in 100 and 21% yields respectively (Scheme 120). In the case of 374, careful purification of the reaction mixture was necessary for, 21% of product **374** to be separated.



Scheme 120: The reduction reaction of 4,4'-dimethylbenzil **371** and furoin **373**

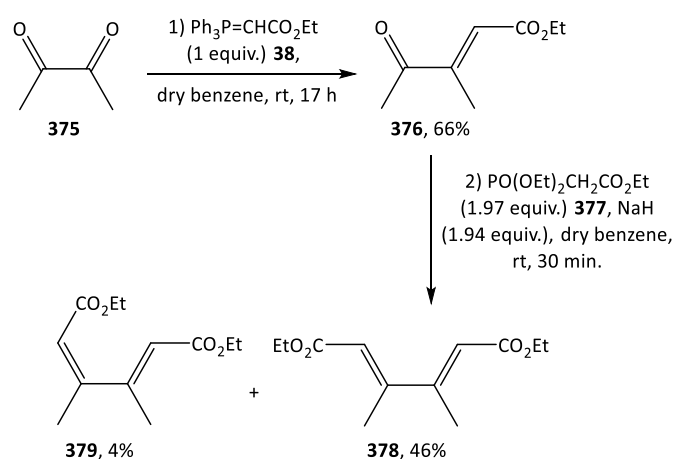
5.6 Attempted synthesis of diene compounds *via* TOP reactions

TOP reaction of vicinal diols with various phosphoranes and in the presence of four commercial oxidants: activated manganese dioxide (MnO_2),⁽¹⁷⁹⁾ iodoxybenzoic acid (IBX),⁽¹⁸⁰⁾ Dess-Martin periodinane (DMP)⁽¹⁹⁾ and pyridine sulfur trioxide complex (SO_3Py) have been studied extensively. The most elegant example of this type of reaction is the oxidation-Wittig reaction of ethylene glycol **42** with MnO_2 , IBX and DMP oxidants leading to the synthesis of α,β -unsaturated diester **43** in 67%, 70% and 27% respectively (Scheme 121).^(76,180)



Scheme 121: The synthesis of dienes *via* TOP reactions^(179, 180, 19)

In 1977, Taylor reported two convenient synthetic procedures to obtain 3,4-unsaturated muconates **378** and **379** *via* the bis-Wittig reaction of butane-2,3-dione **375**.⁽¹⁸¹⁾ The first procedure relied on the reaction of 1,2-diketone **375** with phosphorane ylide **38** in benzene at ambient condition affording the product **376** in 66% yield, followed by the second procedure Wittig reaction of product **376** with Wadsworth-Emmons phosphonate **377** in the presence of sodium hydride producing two isomers **378** and **379** in 46% and 4% respectively (Scheme 122).



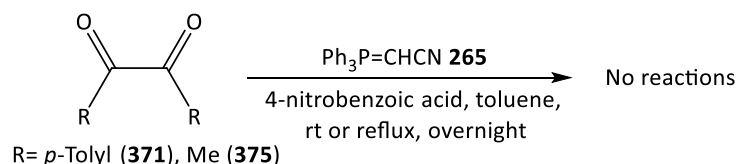
Scheme 122: Taylor's work in 1977 for the synthesis of **378** and **379** isomers

5.7 Access to dienes building blocks *via* Wittig reaction:

Lewis acids are a common condition which has considerable impact on the promotion of Wittig reactions in organic synthesis. Surveys such as that conducted by J. O'Brien *et al* (2013) have shown that 4-nitrobenzoic acid could accelerate the rate of Wittig reaction under mild conditions.^(182a) Therefore, we envisaged that using this additive will be useful to promote our Wittig reaction of diketones with a number of phosphorane ylides in toluene under neutral conditions. Hence, the increased growth of catalytic approaches for classical

Wittig reactions is in high demand by subjecting new catalysts and testing their reactivity later.

Initially, two substrates **375** and **371** were examined to test 4-nitrobenzoic acid discussed below with (triphenylphosphoranylidene)acetonitrile **265**. With **375** and **371** in hand the four conditions shown (Table **18**) were tested. Unfortunately, no evidence was found for the synthesis of desired products from these experiments (Scheme **123**, Table **18**). The treatment of **375** with dry benzene resulted no reaction occurring. Diketone **375** was additionally treated with the combination 4-nitrobenzoic acid /toluene at room temperature which resulted in decomposition of **375**. Whereas, under thermal conditions no reaction occurred. Attempts of converting **371** into the corresponding unsaturated diesters failed even though adding of catalyst (0.4 equiv.).



Scheme 123: Reaction of 1,2-diketones **375** and **371** with cyano ylide

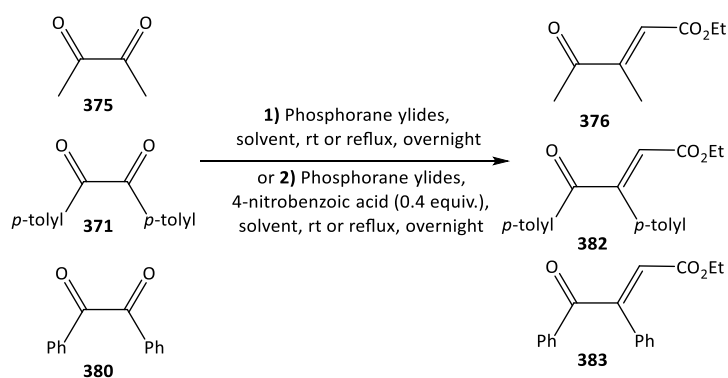
Table 18: Reaction of 1,2-diketones **375** and **371** with cyano ylide

Entry	ketone	Ylide (equiv.)	Catalyst/Condition	Yield
1	Me	3	No catalyst/dry benzene /rt	NR
2	Me	3	4-nitrobenzoic acid (0.2 equiv.) /toluene/rt	Dec.
			4-nitrobenzoic acid (0.2 equiv.) /toluene/ reflux	NR
3	<i>p</i> -tolyl	2.5	4-nitrobenzoic acid (0.4 equiv.) / toluene/ reflux	Dec.

NR means No Reaction, Dec. refers to decomposition

At that point the idea of introducing a cyano ylide *via* Wittig reaction of diketone **371** and **375** was not further pursued. Instead the idea arose of synthetically reacting two phosphorane ylides with diketones (**371**, **375** and **380**).

In contrast, in the presence of ethyl (triphenylphosphoranylidene)acetate **38** with or without 4-nitrobenzoic acid catalyst, formed an α,β -unsaturated esters, afforded the unexpected products in reasonable to good yields (Scheme **124**). Diketones **371**, **375** and **380** were reacted with two different ylides (**381** and **38**). To summarise, it is apparent from all the results, concluded in Table **19**, that the absence of an acid catalyst is beneficial. Furthermore, the phosphorane ester ylides proved to be superior rather than cyano ylide systems. Hence, these were used for all future studies.



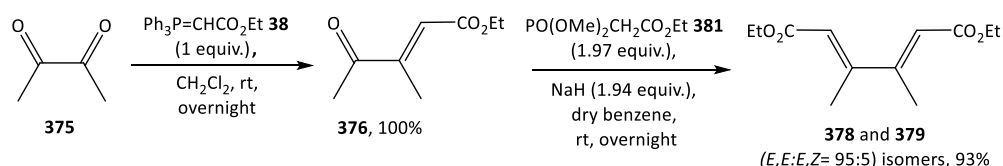
Scheme 124: Attempted Wittig reaction of diketones with and without catalyst

Table 19: Attempted Wittig reaction of diketones with and without catalyst

Entry	ketone	Workup methods	Yield%
1	Me	Ph ₃ P=CHCO ₂ Et 38 (2.2 equiv.)/ CH ₂ Cl ₂ / rt	376 , (100)
2	Me	PO(OMe) ₂ CHCO ₂ Et 381 (3 equiv.)/ MTBD 89 (3.1 equiv.) /toluene/ reflux	NR
3	Me	Ph ₃ P=CHCO ₂ Et 38 (2.2 equiv.)/ dry benzene/ rt	376 , (94)
4	p-tolyl	Ph ₃ P=CHCO ₂ Et 38 (2.5 equiv.)/ 4- nitrobenzoic acid (0.4 equiv.)/ toluene/ reflux	382 , (34)
5	p-tolyl	Ph ₃ P=CHCO ₂ Et 38 (2.2 equiv.)/ dry benzene/ rt	383 , (70)
6	Ph	Ph ₃ P=CHCO ₂ Et 38 (2.5 equiv.)/ 4- nitrobenzoic acid (0.4 equiv.)/ toluene/ reflux	NR
7	Ph	Ph ₃ P=CHCO ₂ Et 38 (2.5 equiv.)/ toluene/ reflux	417 , (31)

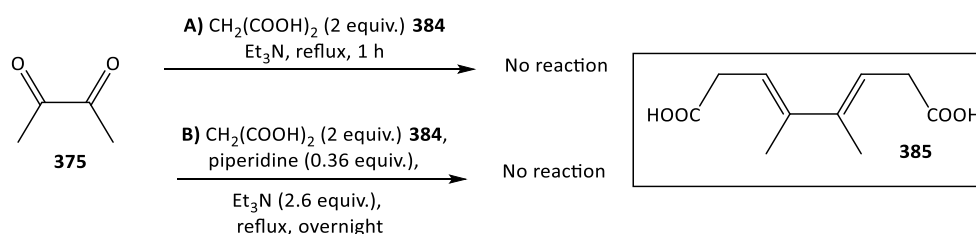
Scheme 125 illustrated the suitable procedure for the synthesis of diethyl (*E,E*) and (*E,Z*)-3,4-dimethylmuconate **378** and **379** from 2,3-butanedione **375** via a sequence of two Wittig steps using olefinating reagents **38** and **381**. By use of

Taylor's procedure, the Wittig reaction was accomplished under the same conditions. However, it was somewhat interesting that the resulting yields in our investigations were higher compared to those of Taylor's study.⁽¹⁸¹⁾



Scheme 125: Bis-Wittig reaction of 2,3-butanedione **375** in two steps

A final reaction was used to investigate whether phosphorane ylides were the problem. In this regard malonic acid was chosen as an alternative to the Wittig reagent, instead phosphorane esters in the presence of triethylamine and piperidine, as shown as in Scheme 126. However, no reaction took place; presumably enolisation of diketone **375** in basic conditions is a problem here.



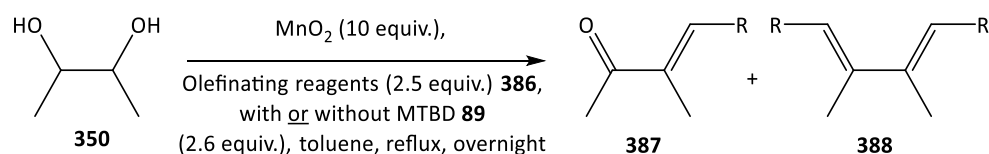
Scheme 126: The alternative substrate for the synthesis of 3,4-unsaturated acid **385**

Based on the successful literature synthesis of 3,4-unsaturated muconates **378** and **379**, we aimed to employ 2,3-butanediol **350** in TOP reaction using different phosphorane ylides in toluene under thermal conditions.

Initially, TOP transformation of 2,3-butanediol **350** to dienes **388** (Scheme 127, Table 20) was investigated as this is a stable and commercially available substrate. These reactions were performed under similar conditions

mentioned in Chapter 2 using manganese dioxide MnO_2 as the first oxidant. However, no reaction was obtained when 2,3-butanediol **350** was treated with phosphorane ylides (Entries **1**, **3**, and **5**). It was envisaged that the desired α,β -unsaturated esters could be observed quickly from 2,3-butanediol **350**.

When the TOP reaction was attempted with alternative ylides (Entries **2**, **4**, and **6**), however, low yields of the products (Entries **2**, **4**, and **6**), were obtained with the major product being the α,β -unsaturated ketones **387**, unreacted starting material **350** and unreacted ylides. Despite changing from THF to toluene, this did not increase the yield of products formed. NMR analysis of the resulted products was confirmed by ^1H -NMR, ^{13}C -NMR and HMRS data.

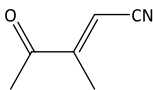
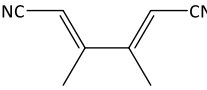
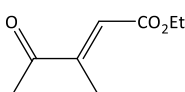
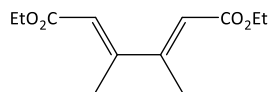
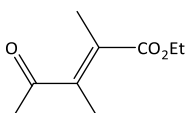
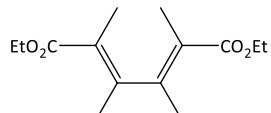
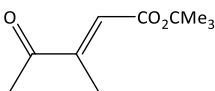
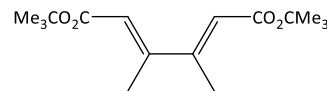
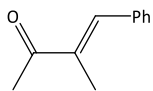
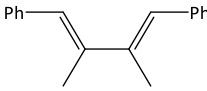
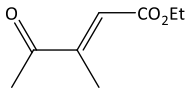
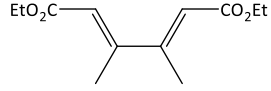


Olefinating reagents **380:**

$\text{Ph}_3\text{P}=\text{CHCN}$ **260**, $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$ **38**,
 $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{CO}_2\text{Et}$ **35**, $\text{Ph}_3\text{P}=\text{CO}_2\text{CMe}_3$ **304**,
 $\text{Ph}_3\text{P}-\text{CH}_2(\text{Br})\text{Ph}$ **316**, $\text{PO}(\text{OMe})_2\text{CH}_2\text{CO}_2\text{Et}$ **381**

Scheme 127: TOP reaction of 2,3-butanediol **350** by manganese dioxide

Table 20: TOP reactions of 2,3-butanediol **350** by manganese dioxide

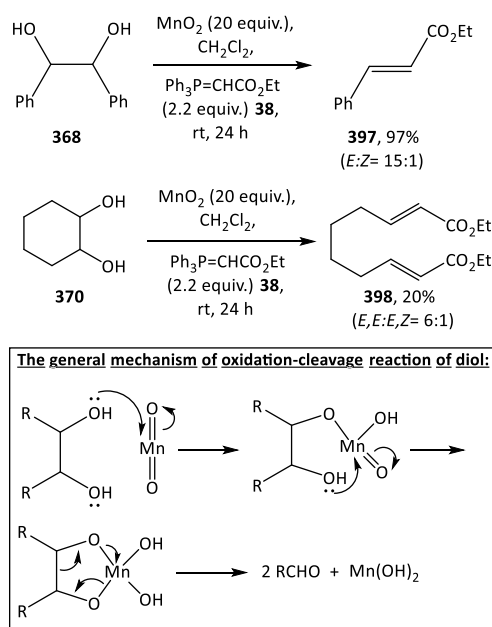
Entry	Olefinating reagents [386]	Yield% [387]	Yield% [388]
1	$\text{Ph}_3\text{P}=\text{CH}\underline{\text{CN}}$ 265	 389, NR	 390, NR
2	$\text{Ph}_3\text{P}=\text{CH}\underline{\text{CO}_2\text{Et}}$ 38	 376, 32	 378, NR
3	$\text{Ph}_3\text{P}=\text{C}(\underline{\text{Me}})\text{CO}_2\text{Et}$ 35	 391, NR	 392, NR
4	$\text{Ph}_3\text{P}=\text{CH}\underline{\text{CO}_2\text{CMe}_3}$ 304	 393, 12	 394, NR
5	$\text{Ph}_3\text{P}-\text{CH}_2(\text{Br})\underline{\text{Ph}}$ 316/ MTBD 89	 395, NR	 396, NR
6	$\text{PO}(\text{OMe})_2\text{CH}_2\underline{\text{CO}_2\text{Et}}$ 381/ MTBD 89	 376, 69	 378, NR

NR= No reaction

With conditions employed for the synthesis of the α,β -unsaturated keto-alkenes above, attention was then turned to use different diols to see if these proved any better. The driving force in this case is the use of a manganese

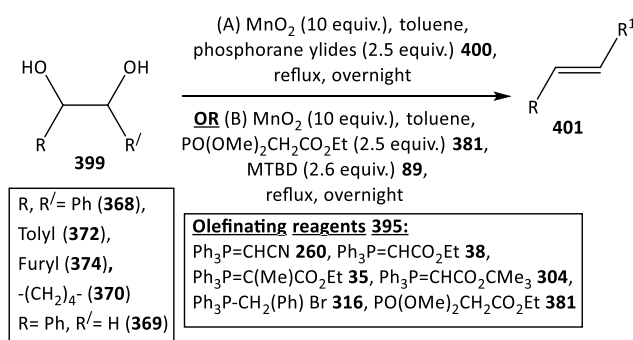
dioxide where it has found the ability of manganese dioxide to oxidise vicinal diols to vicinal diketones by Rice and co-workers.^(182b)

It is interesting to note that in all other substrates (vicinal diols) of this study afforded unexpected products *via* an oxidation-cleavage Wittig reaction. These results are consistent with those of Taylor *et al* (2002) who found that hydrobenzoin **368** and trans-1,2-cyclohexanediol **370** can undergo cleavage-Wittig trapping using phosphorane ylide **38** and manganese dioxide in dichloromethane to afford products **397** and **398** in 97% and 20% yields respectively (Scheme 128).⁽¹⁸³⁾ Scheme 128 shows the general mechanism of oxidation-cleavage step, manganese dioxide (MnO_2) breaks apart 1,2-diols (vicinal diols) to form aldehydes *via* cleaving a C-C bond and forming two C-O π bonds.



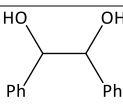
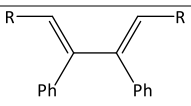
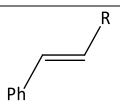
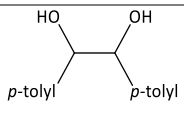
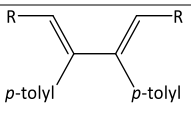
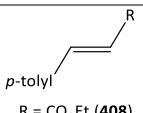
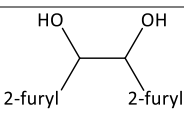
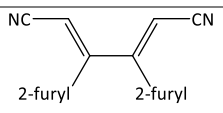
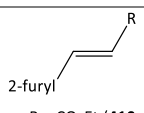
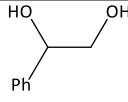
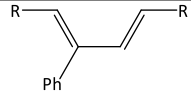
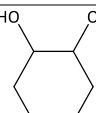
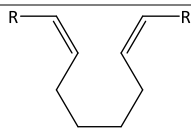
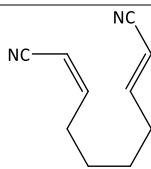
Scheme 128: The oxidation-cleavage Wittig reaction of 1,2-diols according to Taylor⁽¹⁸³⁾

In this project, a variety of 1,2-diols **399** were examined and shown to undergo a cleavage-Wittig sequence. The treatment of **399** with MnO_2 and a number of phosphorane ylides **400** and **381** in toluene furnishes different products **401** (Scheme 129, Table 21).



Scheme 129: The cleavage-Wittig trapping of vicinal diols

Table 21: The cleavage-Wittig trapping of five vicinal diols

Entry ^a	Diol [399]	Desired products	Obtained products
1	 368	 R = CN (402 , 0%) R = Ph (403 , 0%)	 R = CO ₂ Et (397 , 31%) R = CO ₂ Et(Me) (403 , 59%) R = CO ₂ CMe ₃ (404 , 75%)
2	 372	 R = CN (405 , 0%) R = CO ₂ Et(Me) (406 , 0%) R = CO ₂ CMe ₃ (407 , 0%)	 R = CO ₂ Et (408) 100% (method A) and 43% (method B)
3	 374	 409 , 0%	 R = CO ₂ Et (410 , 97%) R = CO ₂ Et(Me) (411 , 54%) R = CO ₂ CMe ₃ (412 , 78%)
4 ^b	 369	 R = CN (413 , 0%) R = CO ₂ CMe ₃ (414 , 0%)	-----
5 ^b	 370	 R = CO ₂ Et (415 , 0%) R = CO ₂ Et(Me) (416 , 0%) R = CO ₂ CMe ₃ (417 , 0%) R = Ph (418 , 0%)	 419 , 37%

(a) All reactions were carried out under method A, compound **408** was synthesised in both methods A and B; (b) Reactions were carried out further with 4-nitrobenzoic acid (0.25 equiv.) in toluene at reflux overnight.

It was somewhat surprising that cyano ylide and phenyl phosphonium salt gave no expected products using MnO₂, while other phosphorane ylides have transformed diols to the corresponding enoate adducts in a range of yields (31-100%), as shown in Table 21. In this line, it was interesting to observe that 2-phenyl-2-hydroxy ethanol **369** (Entry 4) proved to be entirely unsuccessful in this process; in fact, no material could be observed from the reaction,

presumably due to decomposition, perhaps due to phenyl glyoxal. This has been shown previously to react under Wittig conditions only when used with 4Å sieves.⁽¹⁸⁴⁾ Most of these repeated reactions showed the presence of a small amount of starting materials and also unreacted phosphoranes besides the final products.

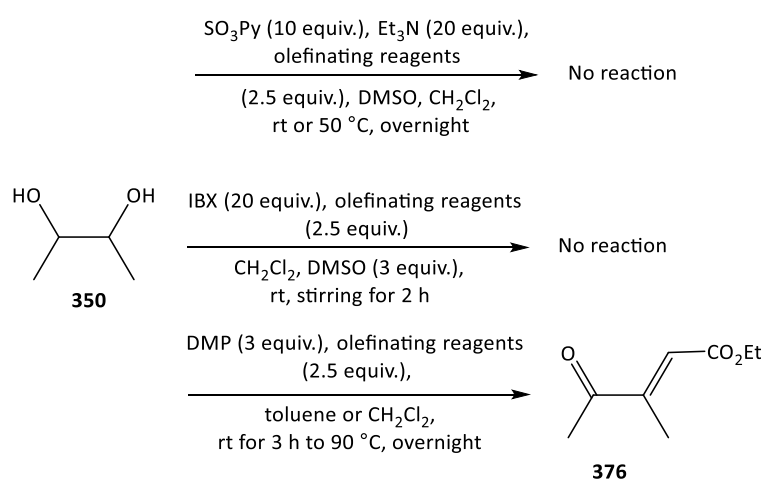
In addition to above, cyclic diols such as 1,2-cyclohexanediol **370** (Entry 5), utilised in this reaction produced only deca-2,8-dienedinitrile **419** in a 37% yield, but the other expected products were not obtained under these conditions.

Though these results indicated that alternative diols and phosphoranes could function in the system, it was apparent that these reactions represented no improvement upon TOP reaction even with the use of 4-nitrobenzoic acid. The search for a new oxidant then moved towards a focused screen of oxidants instead of manganese dioxide that do not promote vicinal diol cleavage.

Iodoxybenzoic acid (IBX), pyridine sulfur trioxide complex (SO₃Py) and Dess-Martin periodinane (DMP) have all been shown in the literature as suitable for the oxidation of 1,2-diols to α,β-diketones. To improve the TOP reaction using these oxidants two substrates were employed and their results compared with manganese dioxide namely 2,3-butanediol **350** and 1,2-diphenylethane-1,2-diol **369**.

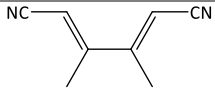
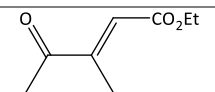
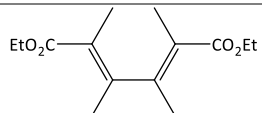
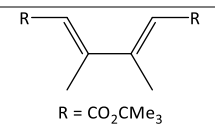
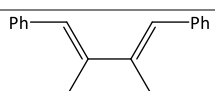
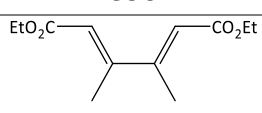
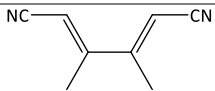
As can be seen in Scheme **130** and Table **22**, most of the attempted procedures failed to afford the expected products. However, it was found that 2,3-butanediol **350** substrate was successfully reacted in one case with Dess-Martin periodinane (DMP) and ethyl (triphenylphosphoranylidene)-acetate **38**

in dichloromethane. The reaction was complete after 15 h to give product **376** in an 11% yield where starting material **350** and ylide **38** were recovered in a large amount compared with the product. This compares to the 32% yield obtained for the synthesis of **376** with MnO_2 . Other phosphoranes did not undergo TOP reaction with 2,3-butanediol **350**; no reaction was observed under their reaction conditions.



Scheme 130: Three attempted procedures for the construction of desired products via TOP reaction of 2,3-butanediol **350** using three different oxidants

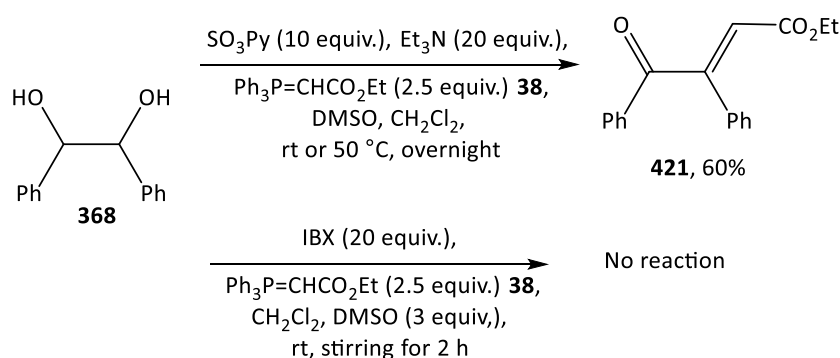
Table 22: Three attempted procedures for the construction of desired products *via* TOP reaction of 2,3-butanediol **350** using three different oxidants

Entry	Olefinating reagents	Oxidants			Products
		SO ₃ Py /Et ₃ N	IBX	DMP	
1	Ph ₃ P=CH <u>CN</u> 265	NR	NR	NR	 390
2	Ph ₃ P=CH <u>CO₂Et</u> 38	NR	NR	11%	 376
3	Ph ₃ P=C(<u>Me</u>) <u>CO₂Et</u> 35	-	-	NR	 392
4	Ph ₃ P=CH <u>CO₂C(CH₃)₃</u> 304	-	-	NR	 394
5	Ph ₃ P-CH ₂ (Br) <u>Ph</u> 316 /MTBD 89	-	-	NR	 396
6	PO(OMe) ₂ CH ₂ <u>CO₂Et</u> 381 /MTBD 89	NR	-	-	 378
7	PO(OEt) ₂ CH ₂ <u>CN</u> 420 /MTBD 89	NR	-	-	 390

NR= No Reaction

Despite these initially disappointing results the more reactive (and more stable) substrate 1,2-diphenylethane-1,2-diol **368** was examined to see if this was more successful. In the TOP reaction of 1,2-diphenylethane-1,2-diol **368** with pyridine sulfur trioxide complex (SO₃Py), (4-oxo-3,4-diphenylbut-2-enoic acid ethyl ester **421** was obtained in 60% (*E*-alkene) yield. No reaction was

observed using IBX, as shown in Scheme 131. Despite this promising result no further investigation of these reactions was attempted.



Scheme 131: The TOP reaction of 1,2-diphenylethane-1,2-diol **368**

To summarise, all the above procedures allow a number of diols to react and generate different products according to the reactivity of these reactions, whereas some of them underwent oxidation and Wittig reactions on both sides and others gave cleavage Wittig reaction affording unexpected products. The next step, the synthesis of such products using 1,2-diketones *via* Wittig reaction will be briefly investigate later.

5.8 Conclusion:

- IMDA-TOP reaction are not feasible due to entropic constraints.
- Tandem TOP-Diels-Alder reactions are not feasible due to difficulty in combining oxidation and olefination for diketones.
- Tandem methods are not more beneficial than stepwise methods in this project.

Chapter 5 Results and Discussion IV: The Pictet-Spengler Cyclisation

6 Introduction: tetrahydro- β -carbolines (TH β Cs):

Tetrahydro- β -carboline moieties are one of the most widely used groups of indole alkaloids and have been extensively used as biologically active compounds; these compounds comprise tricyclic components in its structures. This diversity of ring systems is highlighted by the isolation of tetrahydro- β -carbolines from natural products. Plant and animal systems are the main sources of TH β C compounds, where its biological activities are seen *via* the effect of benzodiazepine receptors on monoamine oxidases.⁽¹⁸⁵⁾ The main aim in this work is to synthesise TH β Cs with different substitution patterns to probe the structure-activity relationships (SAR) *via* the Pictet-Spengler reaction, followed by assaying their biological activities and then comparing them with other alkaloids such as MMV008138 (**422**).⁽¹⁸⁶⁾

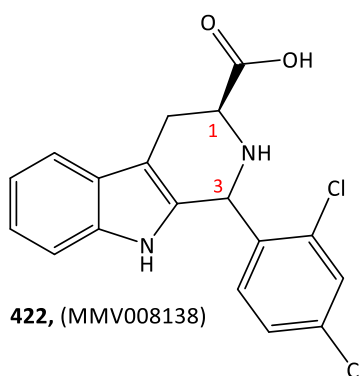
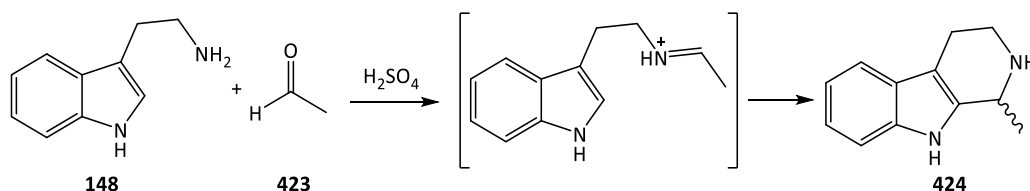


Figure 18: MMV008138 **422** as a TH β C

6.1 Previous studies about tetrahydro- β -carbolines:

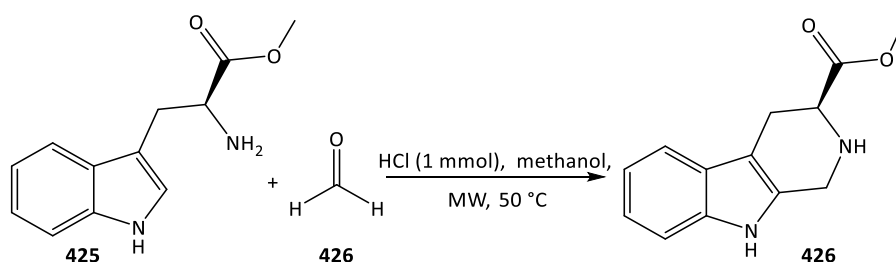
Previous studies on the construction of TH β Cs demonstrated that the most successful approach was the Pictet-Spengler reaction system, a first application

of this reaction was formulated by Tatsui for the synthesis of 1-methyl tetrahydro- β -carboline **424** in the presence of acid catalyst (sulfuric acid); a reaction of tryptamine **148** with acetaldehyde **423** was attempted (Scheme **132**).⁽¹⁸⁷⁾



Scheme 132: The prime example of the synthesis of tetrahydro- β -carboline **424** using the Pictet-Spengler reaction

In chapter one, several popular methodologies were described for synthesising the TH β C system. However, the scope and success of the Pictet-Spengler reaction means other approaches can be. Furthermore, modern conditions reveal the many advantages of using microwave methodology such as short reaction times, ease of isolation and purification, and higher yields. In 2004, Grieco *et al* reported this technique by a reaction of L-tryptophan methyl ester **425** with a variety of aldehydes such as formaldehyde **426** in the presence of methanol and hydrochloric acid (Scheme **133**).⁽¹⁸⁸⁾ It was noticed that the yields are decreased when using other aldehydes such as (4-Cl)- C_6H_4 , (4-CN)- C_6H_4 , (3- NO_2)- C_6H_4 instead of formaldehyde **426**.



Scheme 133: Microwave-assisted Pictet-Spengler reaction

1, 2, 3, 4-Tetrahydro- β -carbolines are one of the most widely used of the indole alkaloids compounds and have been extensively used for pharmacological applications. The past thirty years have seen increasingly rapid advances in the field of the use of TH β Cs in the drug market, therefore, these alkaloids have been in the focus of synthetic efforts for a long time by researchers,⁽¹⁹⁵⁾ and TH β Cs target the mevalonic acid pathway as reported by Odom.^(196a)

The investigation of TH β Cs as antimalarial agents has been an interesting area of interest in our laboratory and around the world. Previous SARs had shown that there is a hydrophobic packet into which the carboxylic acid side chain is orientated and that electron withdrawing groups are required on the phenyl ring^(196a), but little investigation has been made of amides in comparison to others. It was therefore decided to synthesise a series of methyamides with electron withdrawing groups on the phenyl ring to compare their activity to the lead compound **428** (Figure 19).

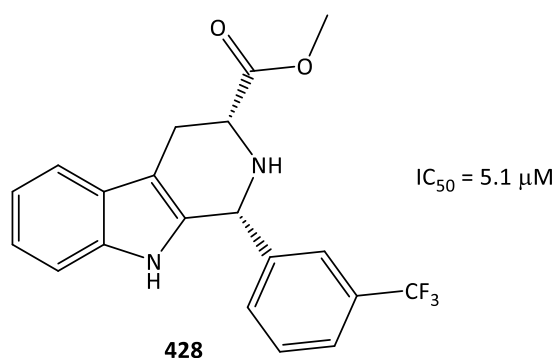


Figure 19: Tetrahydro-β-carbolines **428**

6.2 The Pictet-Spengler Reaction:

Evidence suggests that the Pictet–Spengler reaction is among the most efficient methodologies for two direct steps of the synthesis of tetrahydro-β-carbolines and this has attracted lots of scientists to apply it in organic synthesis.^(189, 185) In particular, the chiral centre at **C-1** allows the stereochemistry at **C-3** to be controlled.

Many factors could affect the determination of the stereochemistry at the new **C-3** chiral centre according to indole alkaloid numbering, as shown in Figure 20.

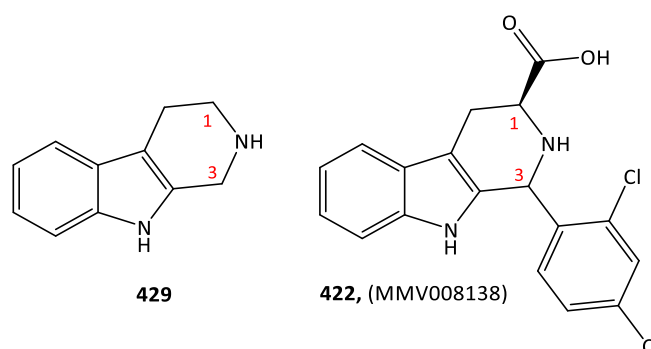


Figure 20: Examples of tetrahydro-β-carbolines

These factors include; the substitution at the β-position of aryl ring, type of both the nucleophilic aromatic species and the amine, the nature of carbonyl compound, the amino group, and finally reaction conditions used.

Basically, the Pictet–Spengler reaction consists of two stages. The first one is the construction of the imine intermediate (Schiff base) through the acid-catalysed imination reaction of β -arylethylamine with carbonyl compounds. Then this imine intermediate undergoes an acid-catalysed cyclisation to afford β -arylethylamide.

As mentioned, the main target in this chapter is to examine the SAR of derivatives of (MMV008138) **422**, the Pictet–Spengler reaction was used to synthesise possible stereoisomers and then assay their biological activities using *Plasmodium falciparum*. The focus was the use of a methyl amine replacement of the carboxylic acid to see this will enhance activity or not. In addition, a variety of electron withdrawing and donating groups such as Cl, CF₃, F, and OCH₃ were investigated to test their effects on the activity of final products.

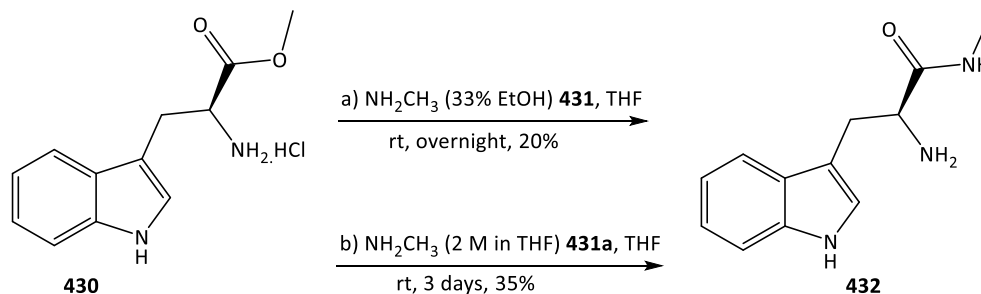
6.3 The synthesis of L-tryptophan methylamide

There is a significant body of literature that recognises the importance of the formation of tetrahydro- β -carbolines *via* the Pictet–Spengler reaction, L-tryptophan methyl ester hydrochloride **430**. Surveys such as that conducted by Rashid (2012), have shown high yields afforded from the reaction of substrate **430** with different aldehydes for the synthesis of *cis/trans* diastereomers.⁽¹⁹⁰⁾

This chapter has been divided into three parts. The first part deals with the synthesis of L-tryptophan methylamide **432**, followed by the Pictet–Spengler cyclisation of the compound **429** to form 1, 2, 3, 4-tetrahydro- β -carbolines.

Finally, test the biological evaluation (antimalarial activity) by measuring IC_{50} of synthesised compounds using *Plasmodium Falciparum*.

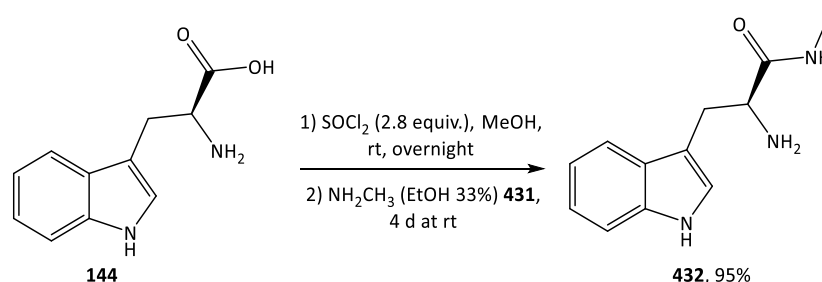
The initial challenge faced was the difficulty of synthesising L-tryptophan methylamide **432** from L-tryptophan methyl ester hydrochloride **430** through a reaction of this ester with ethanolic methylamine solution. Therefore, to examine the effect of the solvent upon the reaction, methylamine was examined in a range of solvents (Scheme **134**). It was observed that no significant difference between the two solutions was evident from the yield of product, where both experiments afforded disappointing yields of about 20 and 35% (Scheme **134**).⁽¹⁹¹⁾ Several repeated experiments revealed low conversion with the starting materials being recovered easily from the reaction *via* column chromatography.



Scheme 134: Initial attempts to synthesise L-tryptophan methylamide **432**

An alternative strategy that could serve to circumvent or at least increase the reactivity of starting material, was employed for the formation the same product in excellent yield. To facilitate this pathway and to maximise the preparation of L-tryptophan methylamide **432**, L-Tryptophan **144** and thionyl chloride was allowed to react in methanol *in situ* by stirring overnight prior to the addition of ethanolic solution of methylamine to afford L-tryptophan

methylamide **432** in a 95% yield according to Tomkinson's procedure (Scheme 135).⁽¹⁹²⁾

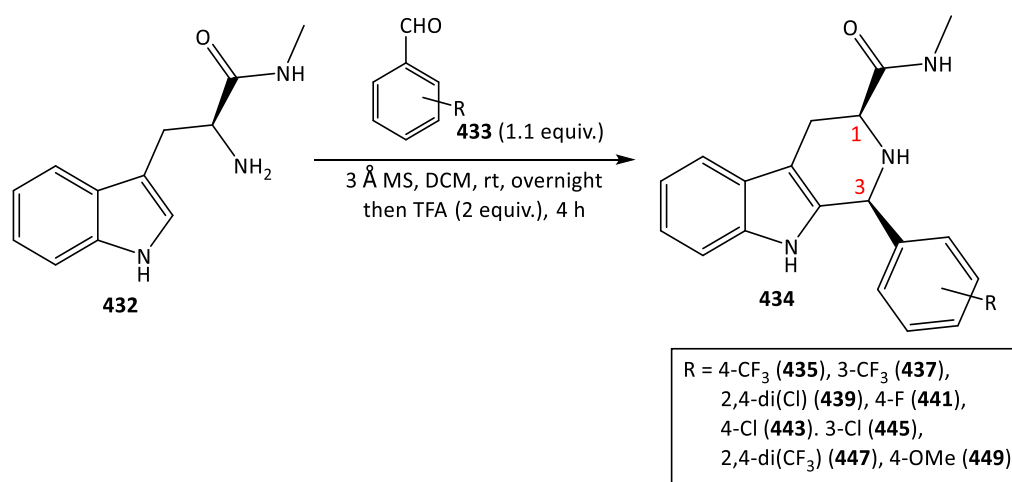


Scheme 135: Alternative method for the synthesis of L-tryptophan methylamide **432**

6.4 The Pictet-Spengler cyclisation reaction of L-Tryptophan methylamide

After the successful formation of L-tryptophan methylamide **432**, the Pictet-Spengler cyclisation was examined through the reaction of amide **432** with a variety of aldehydes in the presence of trifluoroacetic acid and 3 Å molecular sieves in CH₂Cl₂ to form novel indole alkaloids in disappointing yields (5-13%).

The reaction was performed on a 1 equiv. of L-tryptophan methylamide **432** with 1.1 equiv. of aldehydes **433** in dichloromethane, stirred at room temperature overnight and then followed by TLC to check the completion of the imine forming step; the next day the reaction was stirred for 4h after adding 2 equiv. of trifluoroacetic acid. After work-up, the crudes were separated by flash column chromatography to give the tetrahydro-β-carboline products **434**, as shown in Scheme 136 and Table 23.



Scheme 136: The Pictet-Spengler reaction of L-tryptophan methylamide **432**

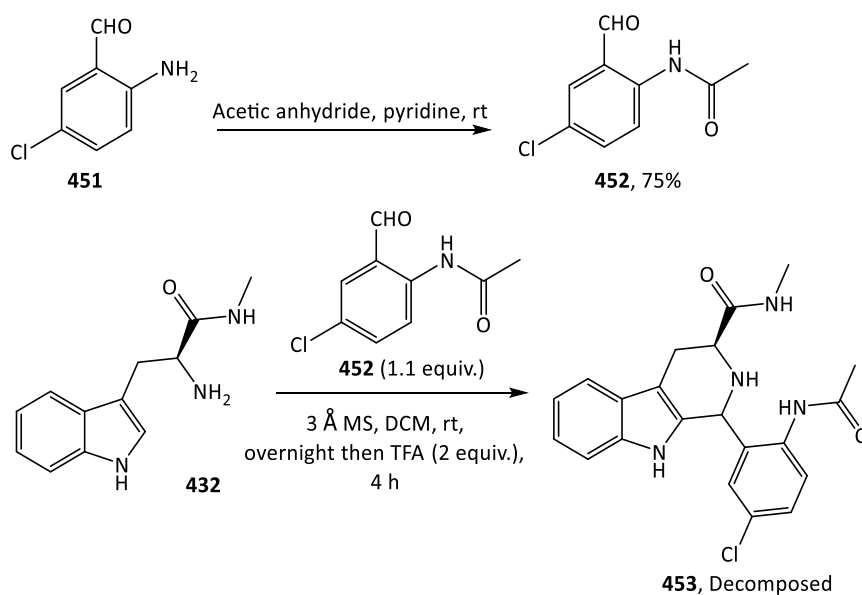
Table 23: The Pictet-Spengler reaction of L-tryptophan methylamide **432**

Entry	Aldehyde [433]/R	Product [434]	¹ H-NMR/ C-3 , 1H	Yield %	Recovery/ SM%
1	4-CF ₃ 435	436	5.25 (s)	13	49
2	3-CF ₃ 437	438	5.23 (t, <i>J</i> = 2.2 Hz)	5	80
3	2,4-(Cl) ₂ 439	440	5.68 (br.s)	7	70
4	4-F 441	442	5.69 (s)	7	42
5	4-Cl 443	444	5.17 (s)	7	34
6	3-Cl 445	446	5.20 (s)	13	52
7	2,4-(CF ₃) ₂ 447	448	5.30 (s)	6	29
8	4-OCH ₃ 449	450	----	0	0

As can be noticed from Table **23** above, with the exception of the 4-methoxy benzaldehyde, which decomposed (entry **8**, Table **23**), it reveals that exclusive *cis*-selectivity (>30:1) and slight improvements in the yield of the products **434** were found under the modified Pictet-Spengler reaction conditions.

All the experiments reviewed above (Scheme **136**, Table **23**), proved the poor reactivity of the starting material (amide **432**) through resulting low yields of the final products even when stirring for extended time. Contrary to expectations, the single most striking observation to emerge from the data comparison with other studies found that just one isomer was isolated and analysed by ^1H -NMR from all these reactions. The NMR spectra of the crude reactions confirmed the appearance of L-tryptophan methylamide **432**, other materials such as aldehydes, a significant amount of impurities and the desired products. Most of the crude mixtures were purified using dichloromethane and diethyl ether as an eluent *via* column chromatography and only diethyl ether solvent was used with the remaining crude reactions. The ^1H -NMR spectrum showed different peaks at a range of 5.17-5.69 ppm. For instance, the bridging CH (C-3 position) group of the product **436** was observed as singlet peaks at 5.25 ppm and 5.81 ppm by NMR analysis.

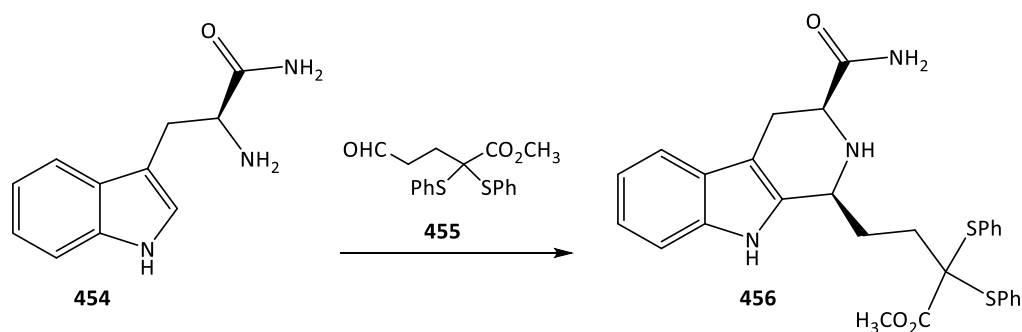
The final area of work upon Pictet-Spengler reactions examined 2-acetamino-5-chlorobenzaldehyde **452** as an alternative aldehyde. At the beginning, a procedure was adapted to synthesise the new aldehyde **452** from the reaction of 2-amino-5-chlorobenzaldehyde **451** with acetic acid in pyridine *via* acetylation reaction, after stirring overnight, affording 2-acetamino-5-chlorobenzaldehyde **452** in a 75% yield, as shown in Scheme **137**.⁽¹⁹³⁾



Scheme 137: The attempted synthesis of 2-acetamino-5-chlorobenzaldehyde via acetylation reaction

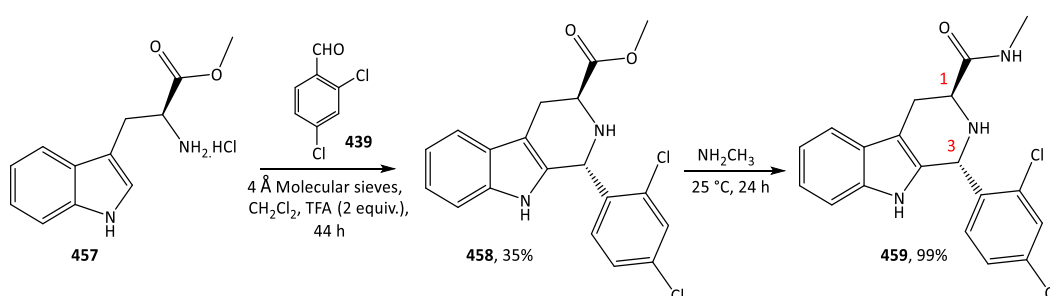
Unfortunately, $^1\text{H-NMR}$ analysis of this crude mixture of the Pictet-Spengler reaction showed only that decomposition of starting material occurred.

It was thought these obtained results related to the poor reactivity of starting material **432**. However, the excellent diastereoselectivity seems to be consistent with the findings of Massiot and Mulamba (1983),⁽¹⁹⁴⁾ who obtained that a pure *cis*-diastereoisomer **456** as the sole product from the reaction of L-tryptophanamide **454** with aldehyde **455**, as shown in Scheme 138.



Scheme 138: The exceptional *cis*-selectivity of L-tryptophanamide **456**

An alternative route would be to carry out a Pictet-Spengler cyclisation on the methyl ester and then convert this to the amide. Carlier *et al* (2015) showed that L-tryptophanmethyl ester salt **457** underwent the Pictet-Spengler cyclisation with 2,4-dichlorobenzaldehyde **439**, followed by treatment of the methyl ester **458** with methylamine to afford good to excellent yields, as shown in Scheme 139.⁽¹⁸⁶⁾ However, such an approach would significantly increase the number of synthetic steps needed so it was discounted.



Scheme 139: the Pictet-Spengler reaction of L-tryptophanmethyl ester salt **457**

6.5 Antimalarial activities of synthesised products

The products synthesised were then screened for antimalarial activity using a 48-hour Dd2Luc *Plasmodium Falciparum* growth inhibition assay, as shown in Figure 21 and Table 24.

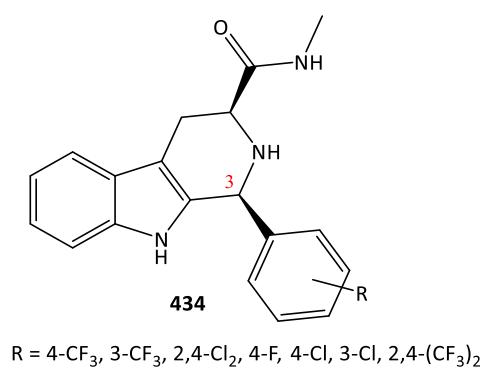


Figure 21: A novel of tetrahydro-β-carboline derivatives

Table 24: A novel of tetrahydro- β -carboline derivatives

Entry	Compounds	R	IC ₅₀ / μ M
1	436	4-CF ₃	> 200
2	438	3-CF ₃	> 200
3	440	2,4-Cl ₂	8.8
4	442	4-F	> 200
5	444	4-Cl	173
6	446	3-Cl	> 200
7	448	2,4-(CF ₃) ₂	> 200

The results obtained were ultimately disappointing. None of the synthesised compounds showed antimalarial activity, with IC₅₀ values greater than 200 μ M these hold of the Dd2Luc assay. This indicates that irrespective of the phenyl substitution pattern, or the EWG present, the amide substituent leads to lower activity than either the lead compound **428** or the original MMV compound **460** (Figure 22). This is somewhat consistent with the observation that examined the replacement of methyl ester precursor with amide group at C-1 substituent was found to be unimportant and no effect on growth inhibitory activity.⁽¹⁸⁶⁾ However, these results were helpful in demonstrating that the amide series of TH β Cs is not a useful avenue of investigation, hence this SAR study was successful.

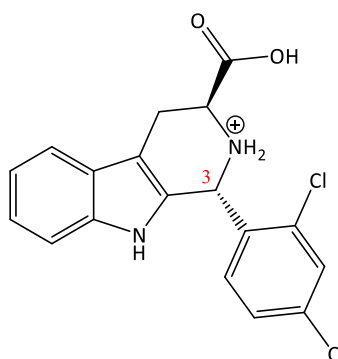


Figure 22: (1R,3S)-MMV008138 stereoisomer **460**

6.6 Conclusion:

- Despite the poor reactivity obtained during the synthesis of L-tryptophanamide **432**, the Pictet-Spengler reactions of L-tryptophanamide were pursued to prepare a novel of indole compounds that examined *via* studying the potency of these substrates against *Plasmodium Falciparum*.
- The results in this chapter indicate that potent antimalarial activity requires a carboxylate/carboxylic acid rather than amide functionality at **C-1**.
- These results seem to be consistent with Carlier's research which found at least one sterically small, electron-withdrawing group at 2' and/or 4 were potent *Plasmodium Falciparum* growth inhibitors.⁽¹⁸⁶⁾

Chapter 6 Experimental section

7 Experimental section

7.1 General experimental details

All commercial solvents were purchased from Sigma Aldrich or Fisher Scientific or VWR chemicals. Anhydrous tetrahydrofuran (THF), *N,N*-dimethylformamide (DMF) and dichloromethane were purchased in anhydrous form. TLC plates used were silica gel 60 F254 (Merck) and detection was conducted by UV light or visualised by potassium permanganate stain followed by gentle warming. Routinely, organic layers were dried over anhydrous MgSO_4 and evaporated using a Büchi evaporator. The determination of melting point (uncorrected) was measured using a Bibby Stuart Scientific Melting point apparatus. All apparatus and metal needles were oven-dried. Most of reactions were conducted under an inert atmosphere using a positive pressure of dry nitrogen or argon gas (using a balloon or bubbler apparatus). In terms of Infrared spectra, the results were recorded on Thermo Nicolet FT-IR Nexus with an Avatar Smart Omni Sampler and diamond crystal. ^1H -NMR and ^{13}C -NMR spectra were run either Avance 300 or Avance 400 instruments in CDCl_3 , d^6 -DMSO or d^4 -MeOH where the results recorded at proton (^1H -300/400 MHz), carbon (^{13}C -75.4/100.5 MHz), phosphorus($^{31}\text{P}\{^1\text{H}\}$ -121.4/161.9 MHz) frequencies. Multiplicity is denoted by: d = doublet; t = triplet; q = quartet; m = multiplet; dd = double doublet; etc. Coupling constants (*J* values) are listed in Hertz (Hz). For the purposes of assignment, the numbering used does not

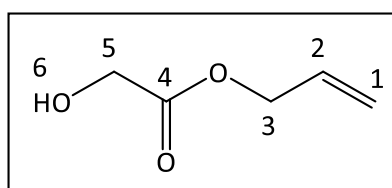
conform to IUPAC nomenclature. Electrospray mass spectroscopy was performed on an Agilent Technology 6530 Accurate-Mass Q-TOF LC/MS machine. Data are reported in the form of (m/z).

For antimalarial activity, 48-hour growth inhibition assays were conducted on the novel compounds to determine their inhibitory concentration (IC_{50}) values. These assays utilised trophozoite stage Dd2Luc *Plasmodium falciparum* parasites. MSF assays were carried out on the candidate compounds that were diluted in a two-fold dilution series using a 60 μ M starting concentration. The data was normalised and plotted as a log-dose response curve to generate IC_{50} values. For all derivatives three independent biological replicates were carried out on assay plates bearing three technical repeats.

7.2 Experimental procedures: Chapter 2

7.2.1 Preparation of esters and amides

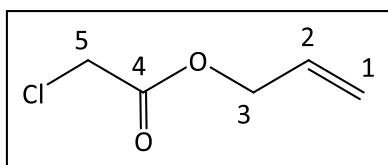
Preparation of allyl glycolate **237**



Glycolic acid **233** (5.00 g, 65.7 mmol, 1 equiv.) was dissolved in toluene (100 mL), and allyl alcohol **231** (4.15 g, 71.5 mmol, $p = 0.854 \text{ g mL}^{-1}$, 4.86 mL, 1 equiv.) added. The solution was acidified with trifluoroacetic acid (149 mg, 1.31 mmol, $p = 1.478 \text{ g mL}^{-1}$, 100 μ L, 0.02 equiv.) added. The resulting mixture was heated to reflux for 3 h with a Dean-Stark head to remove water. The solution was then concentrated to a small volume and then extracted with

saturated sodium bicarbonate (250 mL). The organic layer was washed by water (250 mL), saturated brine (250 mL). The resulting organic layer was dried (MgSO_4) and concentrated *in vacuo*. Drying under high pressure gave yellow oil (3.43 g, 29.6 mmol, 45%). **237**: ^1H -NMR (300 MHz, CDCl_3 , 25 °C): δ = 2.87 (br.s, 1H, H_6), 4.20-4.32 (m, 2H, H_5), 4.67-4.72 (m, 2H, H_3), 5.27-5.39 (m, 2H, H_{1a} , H_{1b}), 5.93 (ddt, J = 16.8, 11.1, 5.8 Hz, 1H, H_2); ^{13}C -NMR (75 MHz, CDCl_3 , 25 °C): δ = 60.6 (C5), 61.1 (C3), 117.7 (C2), 132.2 (C1), 167.5 (C4); Attempts to get high resolution mass spectrometry data failed.

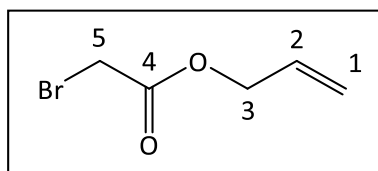
Preparation of allyl chloroacetate **236**:



To a slurry of allyl alcohol **231** (6.30 g, 110 mmol, ρ = 0.854 g mL^{-1} , 7.48 mL, 1 equiv.) in dichloromethane at 0 °C was added pyridine (8.85 g, 112 mmol, ρ = 0.981 g mL^{-1} , 9 mL, 1.01 equiv.) followed by the dropwise addition of chloroacetyl chloride **232** (11.3 g, 100 mmol, ρ = 1.418 g mL^{-1} , 7.96 mL, 0.9 equiv.) over 30 min. The resulting solution was stirred at 0 °C for 15 min and then warmed to room temperature. After the mixture was stirred at room temperature for 24 h, saturated sodium bicarbonate (150 mL) was added. The two layers were stirred for 40 min, and then were separated. The aqueous layer was extracted with dichloromethane (3 \times 150 mL). The organic layers were individually washed with 2 M hydrochloric acid (150 mL) and saturated brine (150 mL), dried (MgSO_4) to afford the product as a yellow oil (7.25 g, 53.8

mmol, 50%). **236**:⁽¹⁹⁷⁾ ¹H-NMR (300 MHz, CDCl₃, 25 °C): δ = 4.08 (s, 2H, H₅), 4.60-4.64 (m, 2H, H₃), 5.19-5.35 (m, 2H, H_{1a}, H_{1b}), 5.80-5.94 (m, 1H, H₂); ¹³C-NMR (75 MHz, CDCl₃, 25 °C): δ = 40.8 (C5), 65.3 (C3), 118.5 (C1), 132.5 (C2), 167.3 (C4); IR (KBr): ν_{max} (cm⁻¹) = 3092, 2960, 2923, 2872, 1759, 1645, 1420, 1382, 1276, 1190, 1090, 988; MS (ESI), 152 (MNH₄⁺), HRMS (ESI, m/z %) calcd. for C₅H₁₁³⁵ClNO₂ [(M+ NH₄)⁺]:152.0478; found: 152.0493, -1.95 ppm error.

Preparation of allyl bromoacetate **238**:



Procedure A:⁽¹⁹⁸⁾

Bromoacetic acid **234** (20.0 g, 143 mmol, 10.3 mL, 1 equiv.) was dissolved in toluene (250 mL), and allyl alcohol **231** (9.13 g, 157 mmol, ρ = 0.854 g mL⁻¹, 10.6 mL, 1.1 equiv.) added. The solution was acidified with trifluoroacetic acid (326 mg, 2.86 mmol, ρ = 1.489 g mL⁻¹, 220 μ L, 0.02 equiv.). The resulting mixture was heated to reflux for 3 h with a Dean-Stark head to remove water. The solution was then concentrated to a small volume and then extracted with saturated sodium bicarbonate (250 mL). The organic layer was washed by water (250 mL) and then saturated brine (250 mL). The resulting organic layer was dried (MgSO₄) and concentrated *in vacuo* and then dried under high pressure to obtain yellow oil (12.7 g, 70.7 mmol, 45%).

Procedure B:⁽¹⁹⁹⁾

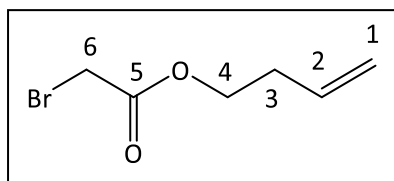
A solution of allyl alcohol **231** (2.00 g, 3.59 mmol, $\rho = 0.854 \text{ g mL}^{-1}$, 2.4 mL, 1 equiv.) and bromoacetic acid **234** (5.00 g, 35.9 mmol, 10 equiv.) was cooled to 0 °C in acetonitrile (200 mL), and 4-(dimethylamino)pyridine (890 mg, 7.19 mmol, 0.2 equiv.) and then dicyclohexylcarbodiimide (8.16 g, 39.6 mmol, 1.1 equiv.) was added. The resulting solution was stirred at room temperature for 24 h. After stirring, the solid was filtered off, washed with acetonitrile (50 mL), and the excess of acetonitrile was evaporated *in vacuo*. The residue was dissolved in dichloromethane (100 mL) and extracted with saturated sodium bicarbonate (100 mL). The organic layer was washed with 2 M hydrochloric acid (100 mL), and then water (100 mL) and finally with saturated brine (100 mL). The final organic layer was dried (MgSO_4) to give the product (40%).

Procedure C:⁽²⁰⁰⁾

To a solution of allyl alcohol **231** (10.0 g, 172.1 mmol, $\rho = 0.854 \text{ g mL}^{-1}$, 11.7 mL, 1 equiv.) and pyridine (13.6 g, 172.1 mmol, $\rho = 0.981 \text{ g mL}^{-1}$, 14.0 mL, 1 equiv.) in dichloromethane (150 mL) at 0 °C, bromoacetyl bromide **235** (34.7 g, 172.1 mmol, $\rho = 2.317 \text{ g mL}^{-1}$, 15.0 mL, 1 equiv.) was added dropwise. The white suspension was stirred at 0 °C for 20 min, followed by 24 hours at room temperature. Water (50 mL) was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 20 mL) and then the combined organic layers were washed with saturated brine (40 mL), dried (MgSO_4), and filtered. The filtrate was then concentrated to give the α -bromoester as yellow oil (30 g, 167.5

mmol, 100%). **238**:^(197b) ^1H -NMR (300 MHz, CDCl_3 , 25 °C): δ = 3.85 (s, 2H, H_5), 4.61 (d, J = 5.8 Hz, 2H, H_3), 5.23 (d, J = 10.4 Hz, 1H, H_1), 5.32 (ddt, J = 17.2 2.5, 2.5 Hz, 1H, H_1), 5.88 (ddt, J = 17.2, 10.4, 5.8 Hz, 1H, H_2); ^{13}C -NMR (75 MHz, CDCl_3 , 25 °C): δ = 42.9 (C5), 64.8 (C3), 119.0 (C1), 132.0 (C2), 165.0 (C4); IR (KBr): ν_{max} (cm^{-1}) = 2962, 1738, 1421, 1279, 1165, 987; GCMS:^(197b) t_{R} = 5.00 min, m/z 180/178 (<1, M^+), 123/121 (100, M^+ -allylO $^+$), 99 (88, M^+ -HBr), 95/93 (53, BrCH_2^+), 85 (53, M^+ - BrCH_2^+), 58 (75, $\text{C}_3\text{H}_6\text{O}^+$), and 57 (90, $\text{C}_3\text{H}_5\text{O}^+$); MS (ESI), 178 (MH^+), HRMS (ESI, m/z %) calcd. for $\text{C}_5\text{H}_8^{79}\text{BrO}_2$ [$(\text{M}+\text{H})^+$]: 178.9707; found: 178.9747, 7.74 ppm error.

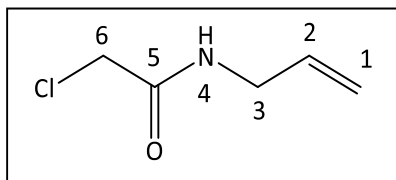
Preparation of 3-butenyl bromoacetate **240**:⁽²⁰¹⁾



To a solution of 3-buten-1-ol **239** (10 g, 138.7 mmol, ρ = 0.838 g mL^{-1} , 11.9 mL, 1 equiv.) and pyridine (10.971 g, 138.7 mmol, ρ = 0.978 g mL^{-1} , 11.2 mL, 1 equiv.) in dichloromethane (100 mL) at 0 °C, bromoacetyl bromide **235** (27.995 g, 138.7 mmol, ρ = 2.317 g mL^{-1} , 12 mL, 1 equiv.) was added dropwise. The suspension was stirred at 0 °C for 20 min, followed by 24 h at room temperature. Water (50 mL) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 \times 20 mL) and then the combined organic layers were washed with brine (40 mL), dried (MgSO_4) and filtered. The solvent was then removed to give 3-butenyl bromoacetate as yellow oil (23.5 g, 116.8 mmol, 88%). **240**: ^1H -NMR (400 MHz,

CDCl₃, 25 °C): δ = 2.43 (q, J = 6.7 Hz, 2H, H₃), 3.84 (s, 2H, H₆), 4.23 (t, J = 6.7 Hz, 2H, H₄), 5.09-5.16 (m, 2H, H₁), 5.74-5.84 (m, 2H, H₂); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 25.9 (C₆), 32.8 (C₃), 65.2 (C₄), 117.6 (C₁), 133.40 (C₂), 167.1 (C₅). IR (neat): ν_{max} (cm⁻¹) = 2980, 1740, 1430, 1290, 1170, 1118; MS (ESI), 192 (MH⁺), HRMS (ESI, m/z %) calcd. for C₆H₁₀⁷⁹BrO₂ [(M+H)⁺]: 192.9864; found: 192.9806, 7.70 ppm error.

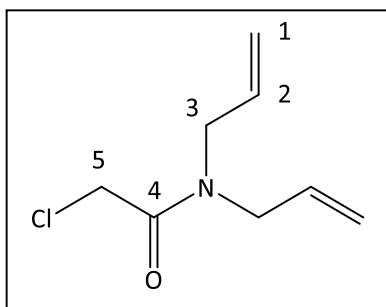
Preparation of *N*-allyl chloroacetamide **245**:



To a slurry of allylamine **241** (6.28 g, 110 mmol, ρ = 0.761 g mL⁻¹, 8.25 mL, 1 equiv.) in dichloromethane (100 mL) 0 °C was added pyridine (8.85 g, 112 mmol, ρ = 0.981 g mL⁻¹, 9 mL, 1.01 equiv.) followed by the dropwise addition of chloroacetyl chloride **232** (11.3 g, 100 mmol, ρ = 1.418 g mL⁻¹, 7.96 mL, 0.9 equiv.) over 30 min. The resulting solution was stirred at 0 °C for 15 min and then warmed to room temperature. After the mixture was stirred at room temperature for 24 hours, saturated sodium bicarbonate (150 mL) was added. The two layers were stirred for 40 min, and then were separated. The aqueous layer was extracted with dichloromethane (3 × 150 mL). The organic layers were individually washed with 2 M aq. hydrochloric acid (150 mL) and saturated brine (150 mL), combined, dried (MgSO₄) to afford the product as yellow oil (9.69 g, 72.5 mmol, 66%). **245**:⁽²⁰²⁾ ¹H-NMR (300 MHz, CDCl₃, 25 °C), NMR showed the presence of a 59:41 mixture of rotamers: δ = 3.75-3.80 (m,

2H, H₃ major, H₃ minor), 3.92 (s, 2H, H₆ major), 3.93 (s, 2H, H₆ minor), 4.00 (s, 2H, H₆), 4.98-5.12 (m, 2H, H_{1a} major, H_{1a} minor, H_{1b} major, H_{1b} minor), 5.19 (s, 1H, H₄ major), 5.20 (s, 1H, H₄ minor), 5.63-5.77 (m, 1H, H₂ major, H₂ minor). ¹³C-NMR (75 MHz, CDCl₃, 25 °C): δ = 42.1 (C3), 42.4 (C6), 116.5 (C1), 133.4 (C2), 166.1 (C5); IR (KBr): ν_{max} (cm⁻¹) = 3296, 3083, 1664, 1545, 1419, 1324, 1261, 1240, 1154, 990, 923, 788, 696, 651, 565; MS (ESI), 134 (MH⁺), HRMS (ESI, m/z %) calcd. for C₅H₉³⁵ClNO [(M+H)⁺]: 134.0372; found: 134.0373, −3.56 ppm error.

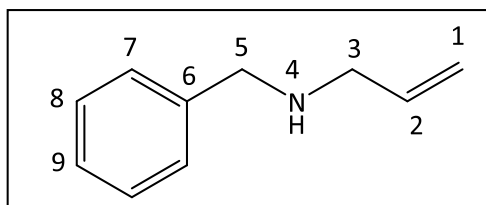
Preparation of *N,N*-diallyl chloroacetamide **246:**



To a slurry of diallylamine **242** (10.7 g, 110 mmol, 13.6 mL, 1 equiv.) in dichloromethane (100 mL) at 0 °C was added pyridine (8.85 g, 112 mmol, ρ = 0.981 g mL⁻¹, 9 mL, 1.01 equiv.) followed by the dropwise addition of chloroacetyl chloride **232** (11.3 g, 100 mmol, ρ = 1.418 g mL⁻¹, 7.96 mL, 0.9 equiv.) over 30 min. The resulted solution was stirred at 0 °C for 15 min and then warmed to room temperature. After the mixture was stirred at room temperature for 24 h, saturated sodium bicarbonate solution (150 mL) was added. The two layers were stirred for 40 min, and then were separated. The aqueous layer was extracted with dichloromethane (3 × 150 mL). The organic layers were individually washed with 2 M aq. hydrochloric acid (150 mL) and saturated brine (150 mL), combined, dried (MgSO₄) to afford the product as

yellow oil (13.3 g, 76.9 mmol, 70%). **246**:⁽²⁰³⁾ ^1H -NMR (300 MHz, CDCl_3 , 25 °C): δ = 3.79-3.86 (m, 4H, H_3), 3.95 (s, 2H, H_5), 4.97-5.12 (m, 2H, H_{1a} , H_{1b}), 5.53-5.75 (m, 2H, H_2). ^{13}C -NMR (75 MHz, CDCl_3 , 25 °C): δ = 41.2 (C5), 50.0 (C6), 118.9 (C1), 132.7 (C2), 166.3 (C4); IR (KBr): ν_{max} (cm^{-1}) = 1660, 1630, 990, 925; MS (ESI), 174 (MH^+), HRMS (ESI, m/z %) calcd. for $\text{C}_8\text{H}_{13}\text{N}^{35}\text{ClO}$ [$(\text{M}+\text{H})^+$]: 174.0685; found: 174.0681, -1.47 ppm error.

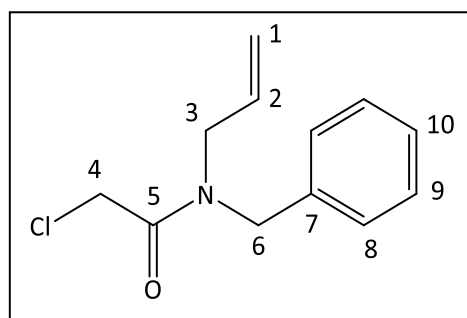
Preparation of *N*-benzylallyl amine **244:**^(204a)



To a suspension of K_2CO_3 (6.98 g, 50.5 mmol, 1.2 equiv.) in allylamine **241** (19.2 g, 337 mmol, ρ = 0.761 g mL^{-1} , 25.3 mL, 8 equiv.) was added benzyl bromide **243** (7.20 g, 42.1 mmol, ρ = 1.438 g mL^{-1} , 5 mL, 1 equiv.) slowly *via* syringe addition over a period of 45 minute. The resulting solution was stirred at room temperature for 24 h. The insoluble solids were filtered off through a celite pad and then rinsed with dichloromethane (100 mL), and the filtrate was then concentrated *in vacuo* to obtain oil. Purification by column chromatography eluting with (hexane/ethyl acetate; 10:1 to 2:1) provided pure *N*-benzylallyl amine as a clear oil (4.33 g, 29.4 mmol, 70%). **244**:^(204a, 204b) ^1H -NMR (300 MHz, CDCl_3 , 25 °C): δ = 2.03 (s, 1H, H_4), 3.30 (d, J = 5.9 Hz, 2H, H_3), 3.81 (s, 2H, H_5), 5.15 (d, J = 10.3 Hz, 1H, H_{1a}), 5.24 (d, J = 17.1 Hz, 1H, H_{1b}), 5.93-6.02 (m, 1H, H_2), 7.26-7.28 (m, 1H, H_9), 7.36 (d, J = 4.6 Hz, 4H, H_7 , H_8); ^{13}C -NMR (75 MHz, CDCl_3 , 25 °C): δ = 51.9 (C3), 53.3 (C5), 115.9 (C1), 127.0 (C2), 128.2 (C7), 128.4 (C8),

137.0 (C9) 140.4 (C6); IR (neat): ν_{\max} (cm^{-1}) = 2925, 2854, 1736, 1454, 1258, 1155, 1104, 1009, 993, 954, 905, 875, 802, 756, 728, 675, 530, 474; MS (ESI), 147(MH^+); HRMS (ESI, m/z %) calcd. for $\text{C}_{10}\text{H}_{13}\text{N}$ [$(\text{M}+\text{H})^+$]: 147.1126; found 147.1132, – 7.17 ppm Error.

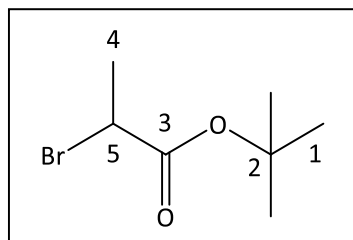
Preparation of *N*-allyl-*N*-benzyl chloroacetamide **247:**



To a slurry of *N*-benzylallyl amine **244** (3.00 g, 20.4 mmol, 1 equiv.) in dichloromethane (50 mL) at 0 °C was added pyridine (1.61 g, 20.4 mmol, $p = 0.981 \text{ g mL}^{-1}$, 1.65 mL, 1.01 equiv.) followed by the dropwise addition of chloroacetyl chloride **232** (20.9 g, 18.5 mmol, $p = 1.418 \text{ g mL}^{-1}$, 1.47 mL, 0.9 equiv.) over 30 min. The resulting solution was stirred at 0 °C for 15 min and then warmed to room temperature. After the mixture was stirred at room temperature for 24 hours, saturated sodium bicarbonate (75 mL) was added. The two layers were stirred for 40 min, and then were separated. The aqueous layer was extracted with dichloromethane (3 × 75 mL). The organic layers were individually washed with 2 M hydrochloric acid (75 mL) and saturated brine (75 mL), dried (MgSO_4), filtered and finally concentrated under vacuum to afford the product as a yellow oil (2.73 g, 12.2 mmol, 60%). **247**:⁽²⁰⁵⁾ ^1H -NMR (400 MHz, CDCl_3 , 25 °C) NMR showed the presence of a 63:37 mixture of rotamers:

δ = 3.89 (dt, J = 5, 1.6 Hz, 1H, H_{3a}), 4.01 (d, J = 5.8 Hz, 1H, H_{3b}), 4.08 (s, 1H, H₄ minor), 4.12 (s, 1H, H₄ major), 4.57 (s, 1H, H₆ minor), 4.60 (s, 1H, H₆ major), 5.15-5.17 (m, 1H, H_{1a}), 5.18-5.23 (m, 1H, H_{1b}), 5.70-5.81 (m, 1H, H₂ major, H₂ minor), 7.18 (d, J = 6.8 Hz, 1H, H₁₀), 7.28-7.30 (m, 2H, H₈ major, H₈ minor), 7.32-7.37 (m, 2H, H₉ major, H₉ minor); ¹³C- NMR (75 MHz, CDCl₃, 25 °C): δ = 41.3 (C₄ major), 41.4 (C₄ minor), 48.4 (C_{3b} minor), 48.7 (C₆ major), 49.4 (C_{3a} major), 50.4 (C₆ minor), 117.5 (C_{1a} major), 118.0 (C_{1b} minor), 126.4 (C₁₀), 127.6 (C₈ minor or C₉ minor), 128.1 (C₈ major or C₉ major), 128.9 (C₈ minor or C₉ minor), 129.0 (C₈ major or C₉ major), 132.0 (C₂ minor), 132.3 (C₂ major), 135.9 (C₇ minor), 136.7 (C₇ major), 166.8 (C₅ minor), 170.0 (C₅ major); IR (KBr): ν_{max} (cm⁻¹) = 3064, 3029, 2921, 1653, 1605, 1451, 1244, 1140, 1028, 993, 954, 926, 860, 794; MS (ESI), 224 (MH⁺), HRMS (ESI, m/z %) calcd. for C₁₂H₁₅N³⁵ClO [(M+H)⁺]: 224.0842; found: 224.0830, 3.16 ppm error.

Preparation of *tert*-butyl 2-bromopropionate 247a:



Procedure A:⁽²⁰⁶⁾

To a cooled 0 °C solution of 2-bromopropionic acid (2.00 g, 13.07 mmol, ρ = 1.70 g mL⁻¹, 1.17 mL, 1 equiv.), 4-(dimethylamino)pyridine (1.27 g, 10.4 mmol, 0.8 equiv.) and *tert*-butyl alcohol (2.90 g, 39.21 mmol, ρ = 1.387 g mL⁻¹, 200 μ L, 3 equiv.) were dissolved in dichloromethane (30 mL). The mixture was stirred vigorously at 0 °C, and then a solution of DCC (2.96 g, 14.3 mmol, 1.1 equiv.) in

dichloromethane (5 mL) was added slowly. The resulted solution was stirred at room temperature for 15 h. The precipitate formed was filtered through celite and washed with dichloromethane (50 mL). The extract was washed with saturated sodium bicarbonate (100 mL), brine (150 mL), dried (MgSO₄), filtered and then concentrated *in vacuo* to afford the crude **247a**, as yellow oil, which was used without further purification. No characterisation of **247a** was attempted in this procedure.

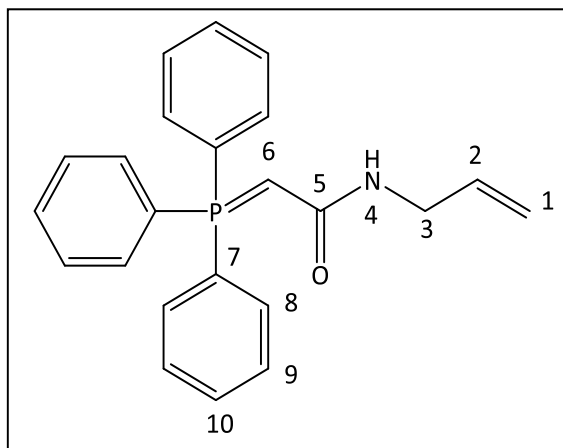
Procedure B:

To a cooled (-78 °C) round flask of a dry ice/acetone bath, Isobutylene was bubbled into this round until collecting (10 mL) of liquid isobutylene. A solution of 2-bromopropionic acid (5.00 g, 32.6 mmol, $\rho = 1.70 \text{ g mL}^{-1}$, 2.9 mL, 1 equiv.) was dissolved in dichloromethane (80 mL) then added dropwise to liquid isobutylene. After 5 min, concentrated sulphuric acid (500 μL) was added. The resulting solution was stirred for 16 hours. Saturated aq. sodium bicarbonate (50 mL) was added. The extract was separated and washed with saturated sodium bicarbonate solution (50 mL), water (50 mL) and brine (50 mL), then dried (MgSO₄). The filtrate was concentrated *in vacuo* to give a pure colourless liquid **247a** (4.0 g, 19.2 mmol, 58.8%). **247a**:⁽²⁰⁷⁾ ¹H-NMR (300 MHz, CDCl₃, 25 °C): $\delta = 1.48$ (s, 9H, H₁), 1.79 (d, $J = 6.9 \text{ Hz}$, 3H, H₄), 4.27 (q, $J = 6.9 \text{ Hz}$, 1H, H₅); ¹³C-NMR (75 MHz, CDCl₃, 25 °C): $\delta = 21.6$ (C1), 27.7 (C4), 41.9 (C5), 82.1 (C2), 169.2 (C3); IR (neat): ν_{max} (cm⁻¹) = 3342, 2974, 2930, 2900, 1734, 1457, 1370, 1236, 1148, 1046, 844, 755, 714, 683; MS (ESI), 207 (MH⁻), HRMS (ESI, m/z %) calcd for C₇H₁₂⁷⁹BrO₂ [(M-H)⁻]:⁽²⁰⁶⁾ 207.0021, found 207.0023.

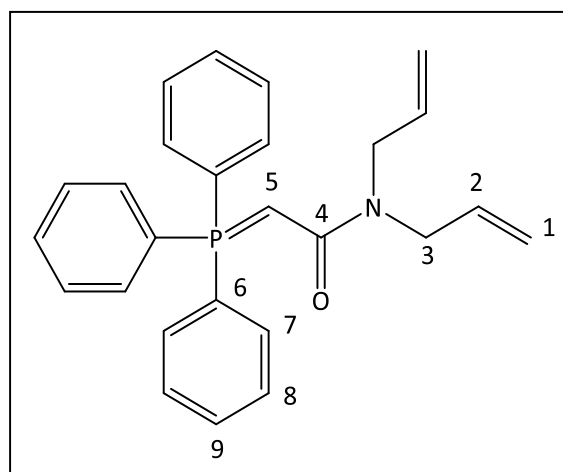
7.2.2 Preparation of phosphorane ylides

General procedure 1:

Halo ester (1 equiv.) was dissolved in acetonitrile and triphenylphosphine (1.02 equiv.) was added. The mixture was stirred and heated at reflux under nitrogen pressure for (16 hours) after that cooled to room temperature and concentrated *in vacuo*. The resulting viscous residue was dissolved in a mixture of benzene (50 mL) and hexane (50 mL) and washed with water (150 mL). Two drops of alcoholic phenolphthalein were added as an indicator and then the solution was extracted with ether (150 mL). The aqueous solution was stirred vigorously and cooled in an ice bath. Drops of 2 M sodium hydroxide solution were added slowly until the pink end-point was reached (pH 8–10). The solid was collected by filtration, washed thoroughly with cold water, and dried over phosphorus pentoxide to obtain the desired phosphoranes. Conversion was determined by analysis of the ^1H -NMR spectrum.

Preparation of *N*-allyl(triphenylphosphoranylidene) acetamide 251:

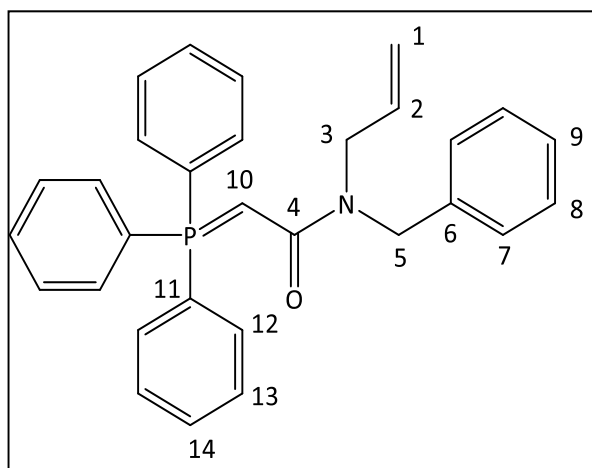
According to **general procedure 1** using allyl chloroacetate **245** (1.33 g, 9.95 mmol, 1equiv.), acetonitrile (25 mL) and triphenylphosphine (2.66 g, 10.15 mmol, 1.02 equiv.) were combined to give the crude **251**, as white solid, which was used without further purification. No characterisation of **251** was attempted in this procedure because of its decomposition.

Preparation of *N,N*-diallyl(triphenylphosphoranylidene) acetamide 252:

According to **general procedure 1** using *N,N*-diallyl chloroacetamide **246** (1.73 g, 9.99 mmol, 1 equiv.), acetonitrile (50 mL) and triphenylphosphine (2.67 g, 10.2 mmol, 1.02 equiv.) were combined. The title compound **252** was obtained

as faint white solid (2.58 g, 6.43 mmol, 65%). **252**:⁽²⁰⁸⁾ m.p. 95-96 °C; ¹H-NMR: (400 MHz, CDCl₃, 25 °C): δ = 2.87 (d, J_{PH} = 22.4 Hz, 1H, H₅), 3.97 (d, J = 5.4 Hz, 2H, H₃), 5.11 (d, J = 10.3 Hz, 2H, H_{1a}), 5.17 (d, J = 17.4 Hz, 2H, H_{1b}), 5.88 (ddt, J = 17.4, 10.3, 5.4 Hz, 2H, H₂), 7.43-7.48 (m, 6H, H₈), 7.53 (td, J = 7.1, J_{PH} = 1.1 Hz, 3H, H₉), 7.69 (dd, J_{PH} = 12.3, J = 7.1 Hz, 6H, H₇); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 31.1 (d, J_{PC} = 131 Hz, C5), 48.9 (s, C3), 115.2 (s, C1), 128.5 (d, J_{PC} = 12.0 Hz, C7), 131.4 (d, J_{PC} = 2.8 Hz, C9), 132.1 (d, J_{PC} = 9.9 Hz, C6), 133.0 (d, J_{PC} = 9.9 Hz, C8), 135.9 (s, C2), 172.0 (s, C4); ³¹P{¹H}-NMR (162 MHz, CDCl₃, 25 °C): δ = 17.7 (s). IR (neat): ν_{max} (cm⁻¹) = 696, 720, 779, 856, 922, 984, 1072, 1118, 1142, 1359, 1437, 1470, 1495, 1633, 2914; MS (ESI), 400 (MH⁺), HRMS (ESI, m/z %) calcd. for C₂₆H₂₇NOP [(M+H)⁺]: 400.1830; found: 400.1838, -2.37 ppm error.

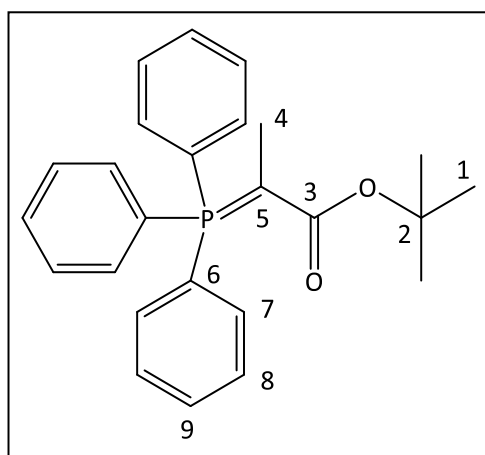
Preparation of *N*-allyl-*N*-benzyl (triphenylphosphoranylidene) acetamide **253:**



According to **general procedure 1** using *N*-allyl-*N*-benzyl chloroacetamide **247** (4.3 g, 19.2 mmol, 1 equiv.), acetonitrile (100 mL) and triphenylphosphine (4.78 g, 19.6 mmol, 1.02 equiv.) were combined to afford the product as thick yellow oil (2.84 g, 6.53 mmol, 34%). **253**:⁽²⁰⁸⁾; ¹H-NMR (400 MHz, CDCl₃, 25 °C):

δ = 2.93 (br. s, 1H, H₁₀), 3.93-3.97 (m, 2H, H₃), 4.60 (s, 2H, H₅), 5.09-5.19 (m, 2H, H_{1a}, H_{1b}), 5.88 (ddt, J = 16.4, 10.7, 5.2 Hz, 1H, H₂), 7.22-7.33 (m, 5H, H₇, H₈, H₉), 7.42-7.49 (m, 6H, H₁₂), 7.51-7.57 (m, 3H, H₁₄), 7.66-7.74 (m, 6H, H₁₃); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 48.1 (C3), 49.1 (C5), 115.6 (C1), 126.5 (C9), 127.7 (C7), 128.2 (C8), 128.5 (J_{PC} = 3.3 Hz, C13), 128.7 (J_{PC} = 3.3 Hz, C13), 129.9 (C11), 131.5 (C14), 133.1 (J_{PC} = 9.9 Hz, C12), 135.4 (C2), 140.2 (C6), 172.2 (C4); ³¹P{¹H}-NMR (162 MHz, CDCl₃, 25 °C): δ = 17.8 (s); IR (neat): ν_{\max} (cm⁻¹) = 3060, 2951, 1636, 1496, 1438, 1356, 1246, 1195, 1121, 997, 911, 742, 695; MS (ESI), 450 (MH⁺), HRMS (ESI, m/z %) calcd. for C₃₀H₂₉NOP [(M+H)⁺]: 450.1986; found: 450.2016, – 4.92 ppm error.

Preparation of tert-butyl 2-(triphenylphosphoranylidene)propionate 305:



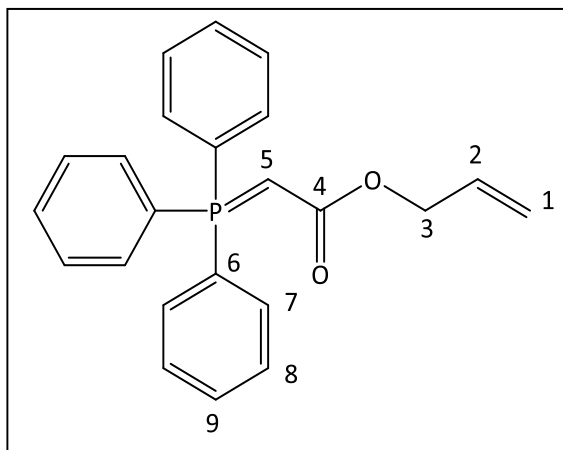
According to **general procedure 1** using *tert*-butyl-2-bromopropionate **247a** (4.0 g, 19.13 mmol, 1 equiv.), acetonitrile (100 mL) and triphenylphosphine (5.11 g, 19.51 mmol, 1.02 equiv.) were combined to afford the product as thick red oil (2.5 g, 6.4 mmol, 33%). **305**:^(209a); ¹H-NMR (400 MHz, CDCl₃, 25 °C): δ = 0.96 (s, 9H, H₁), 1.63 (m, 3H, H₄), 7.41-7.48 (m, 6H, H₇), 7.50-7.57 (m, 3H, H₉), 7.60-7.66 (m, 6H, H₈); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 12.6 (C4), 28.6

(C1), 55.3 (C2), 97.3 (C5), 128.3 (d, $J = 11.7$ Hz, C7), 131.4 (d, $J = 2.9$ Hz, C9), 133.7 (d, $J = 9.5$ Hz, C8); IR (neat): ν_{\max} (cm^{-1}) = 3049, 2977, 2900, 1712, 1590, 1474, 1439, 1252, 1182, 1025, 844, 785, 752, 712, 697; MS (ESI), 391 (MH^+), HRMS (ESI, m/z %) calcd. for $\text{C}_{25}\text{H}_{28}\text{O}_2\text{P}$ [$(\text{M}+\text{H})^+$]: 391.1826; found: 391.1823, – 0.63 ppm error.

7.2.3 The preparation of phosphorane ylides

General procedure 2:

To a solution of triphenylphosphine (1 equiv.) in toluene, halo ester (1 equiv.) was added dropwise to form a slurry. This slurry was stirred overnight and then filtered and washed with toluene (30 mL) and hexane (50 mL) to give the corresponding phosphonium salt as a white solid. The salt was dissolved in water (100 mL) and 2 M sodium hydroxide solution was added to keep the aqueous solution at a $\text{pH} < 7$, while a white precipitate formed. The reaction mixture was then stirred for 30 min and then dichloromethane (50 mL) was added to dissolve the precipitate. The organic layer was separated, washed with brine (50 mL), dried (MgSO_4) and filtered. The filtrate was then concentrated and dried to give the desired phosphorane.

Preparation of allyl (triphenylphosphoranylidene) acetate **248:****Procedure A:**

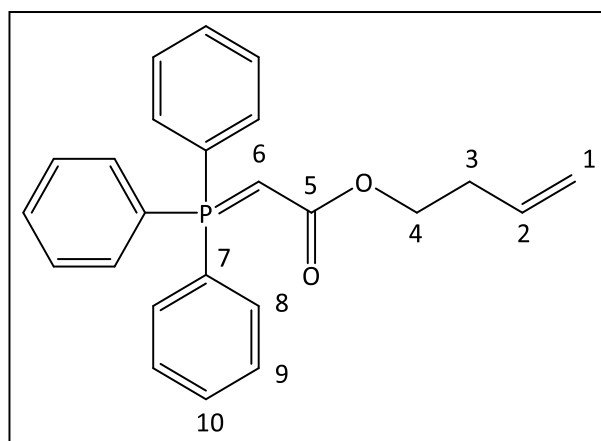
According to **General procedure 2** using triphenylphosphine (47.39 g, 180.7 mmol, 1equiv.), toluene (50 mL) and allyl bromoacetate **238** (32.36 g, 180.7 mmol, 1 equiv.) The phosphorene was obtained as thick red oil (44.9 g, 124.6 mmol, 70%). **248**: $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 $^\circ\text{C}$): δ = 3.23 (br. s, 1H, H_5), 4.45 (d, J = 4 Hz, 2H, H_3), 4.94-5.22 (m, 2H, H_1), 5.70-5.79 (m, 1H, H_2), 7.43-7.49 (m, 6H, H_8), 7.54-7.58 (m, 3H, H_9), 7.64-7.71 (m, 6H, H_7); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3 , 25 $^\circ\text{C}$): δ = 53.6 (C5), 63.5 (C3), 116.5 (C1), 128.9 (J_{PC} = 12.1 Hz, C7), 132.3 (C9), 133.0 (J_{PC} = 9.9 Hz, C8), 134.3 (C6), 137.8 (C2), 170.4 (C4); IR (neat): ν_{max} (cm^{-1}) = 3052, 2978, 2925, 1716, 1587, 1477, 1436, 1364, 1102, 1062, 871, 749, 732, 691; MS (ESI), 361 (MH^+), HRMS (ESI, m/z %) calcd. for $\text{C}_{23}\text{H}_{22}\text{O}_2\text{P}$ [$(\text{M}+\text{H})^+$]: 361.1357; found: 361.1370, – 4.74 ppm error.

Procedure B:

To a solution of triphenylphosphine (4.96 g, 0.018 mmol, 1equiv.) in trifluoroacetic acid (7 mL), allyl glycolate **237** (2.0 g, 0.017 mmol, 1 equiv.) was added dropwise. This solution was stirred overnight at reflux and then added and water (30 mL) and dichloromethane (50 mL). The organic layer was separated and dried (MgSO_4), the filtrate was then concentrated *in vacuo* to give the crude **248**, as white solid, which was used without further purification. No characterisation of **248** was attempted in this procedure because its decomposition.

Preparation of 3'-butyen-1'-yl 2-(triphenylphosphoranylidene)acetate

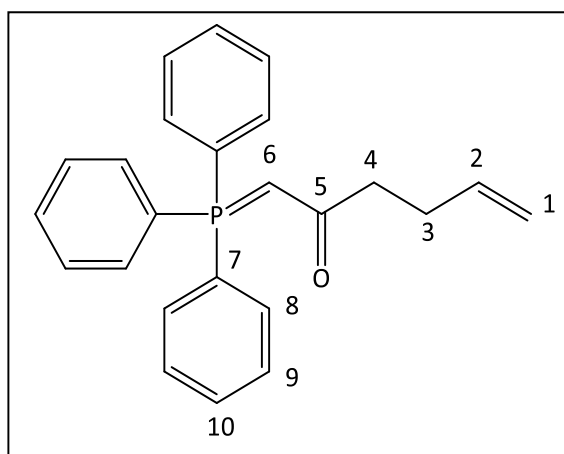
254:^(209b)



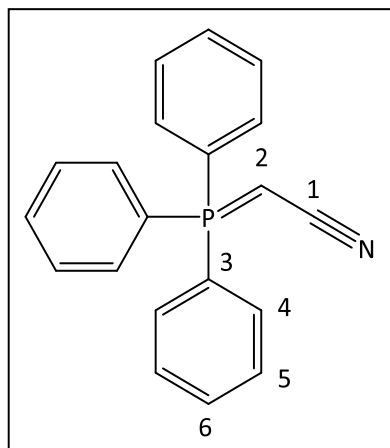
According to **General procedure 2** using triphenylphosphine (31.9 g, 122 mmol, 1 equiv.), toluene (50 mL) and 3-butenyl bromoacetate **240** (23.5 g, 122 mmol, 1 equiv.) to afford the phosphorane as thick red oil (31.97 g, 85.4 mmole, 70%). **254**: $^1\text{H-NMR}$ (400 MHz, CDCl_3 , 25 °C): δ = 2.14-2.18 (m, 2H, H_3), 2.93 (br.s, 1H, H_6), 3.97 (t, J = 6.8 Hz, 2H, H_4), 4.89-4.98 (m, 2H, H_1), 5.65 (br.s, 1H, H_2), 7.42-7.70 (m, 15H, H_8 , H_9 , H_{10}); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 25 °C): δ = 30.2 (d, 124 Hz, C_1), 33.9, 61.5, 116.0, 124.5, 128.6, 128.8, 131.9, 132.0, 132.1,

133.0, 133.1, 135.5, 171.1 (C5); $^{31}\text{P}\{^1\text{H}\}$ -NMR (162 MHz, CDCl_3 , 25 °C): δ = 18.04 (s); IR (neat): ν_{max} (cm^{-1}) = 3058, 2941, 1726, 1482, 1455, 1435, 1394, 1334, 1144, 1105, 1063, 997, 880, 717, 689; MS (ESI), 375 (MH^+), HRMS (ESI, m/z %) calcd. for $\text{C}_{24}\text{H}_{24}\text{O}_2\text{P}$ [$(\text{M}+\text{H})^+$]: 375.1513; found: 375.1529, -5.28 ppm error.

Preparation of 1-(triphenylphosphoranylidene)-5-hexen-2-one 444:^(210a)



To a cooled solution of triphenylphosphoranylidene acetone (2.5 g, 7.85 mmol, 1 equiv.) in anhydrous THF (125 mL), *n*-butyllithium solution [1.6 M in hexanes] (5.88 mL, 9.42 mmol, 1.2 equiv.) was added at -78 °C and the mixture was stirred for 30 min. Allyl bromide (1.139 g, 9.42 mmol, $\rho = 1.398$ g mL^{-1} , 810 μL , 1.2 equiv.) was then added and the reaction left to warm to room temperature slowly. The reaction mixture was quenched with water (100 mL) and extracted with dichloromethane (2×100 mL), washed with brine (300 mL), dried over (MgSO_4) and concentrated under reduced pressure affording white solid. No characterisation of desired ylide was attempted.

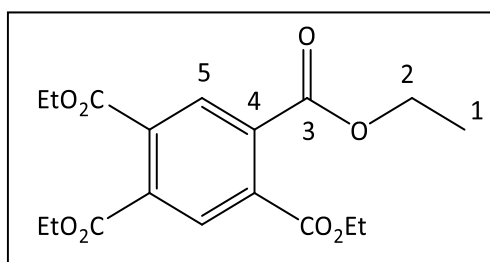
Preparation of (cyanomethyl)triphenylphosphonium bromide **265**:

To a solution of bromoacetonitrile (10.00 g, 166.7 mmol, $\rho = 1.722 \text{ g mL}^{-1}$, 5.80 mL, 1 equiv.) in toluene (150 mL) was added a solution of triphenylphosphine (21.86 g, 166.7 mmol, 1 equiv.) in toluene (50 mL). The reaction was set aside for 3 days at room temperature. The white precipitate was filtered and washed thoroughly with toluene ($2 \times 50 \text{ mL}$) and then hexane ($3 \times 50 \text{ mL}$) to give the phosphonium salt. The salt (5.00 g, 13.08 mmol, 1 equiv.) was dissolved in dichloromethane (100 mL) and then extracted with 2 M potassium hydroxide solution ($3 \times 50 \text{ mL}$). The collected organic layers washed with saturated brine (100 mL), dried (MgSO_4), filtered and concentrated *in vacuo* to afford the desired ylide **265** as a white solid (3.8 g, 12.6 mmol, 96%) which was recrystallised from (10 mL) of boiling hexane. **265**:^(210b) m.p. 178-183 °C; ^1H -NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 7.43\text{--}7.54$ (7H, m, H_2 , H_5), 7.56-7.69 (9H, m, H_6 , H_4); ^{13}C -NMR (75.4 MHz, CDCl_3 , 25 °C): $\delta = -2.0$ (d, $J_{\text{PC}} = 135 \text{ Hz}$, C5), 127.4 (d, $J_{\text{PC}} = 91.8 \text{ Hz}$, C4), 128.1 (d, $J_{\text{PC}} = 7.7 \text{ Hz}$, C6), 129.1 (d, $J_{\text{PC}} = 12.4 \text{ Hz}$, C3), 132.6 (d, $J_{\text{PC}} = 3.1 \text{ Hz}$, C1), 132.8 (d, $J_{\text{PC}} = 9.9 \text{ Hz}$, C2); $^{31}\text{P}\{^1\text{H}\}$ -NMR (121.4 MHz, CDCl_3 , 25 °C): $\delta = 24.18$ (s); IR (KBr): ν_{max} (cm^{-1}) = 3054, 3012, 2987, 2138, 1583,

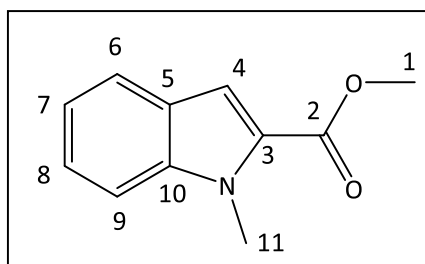
1483, 1435, 1334, 1310, 1260, 1190, 1187, 1147, 1105, 1067, 1028, 997, 842, 765, 715, 693; MS (ESI), 302 (MH^+), HRMS (ESI⁺) calcd. for $C_{20}H_{17}NP$ [$(M+H)^+$]: 302.1098; found 302.1103, -0.66 ppm error.

7.2.4 Preparation of ester derivatives

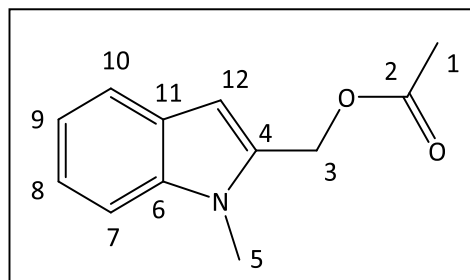
Preparation of tetraethylpyromellitate **210**:⁽¹¹⁴⁾



Pyromellitic acid **209** (5.00 g, 3 mol, 1 equiv.) was esterified with ethanol (11 mL), toluene (40 mL) and sulphuric acid (60 μ L) using a Dean-Stark head to remove water, heating at $165^\circ C$ for (2-15 h). Then after the mixture was cooled to room temperature, water (100 mL) was added and the solution was extracted with a further dichloromethane (3×100 mL). The extracts were washed with saturated sodium bicarbonate solution (100 mL) and water (100 mL), and then dried over ($MgSO_4$). The solvent was removed under higher vacuum to give a yellow liquid (2.16 g, 5.89 mmol, 30%). **210**:^(211a); 1H -NMR (300 MHz, $CDCl_3$, $25^\circ C$): δ = 1.39 (t, J = 7.0 Hz, $4CH_3$, H_1), 4.36 (q, J = 7.0 Hz, $4CH_2$, H_4), 8.02 (s, 2H, H_5); ^{13}C -NMR (75 MHz, $CDCl_3$, $25^\circ C$): δ = 14.1 ($C1$), 62.1 ($C2$), 134.2 ($C2$), 137.8 ($C5$), 165.0 ($C3$); IR (KBr): ν_{max} (cm^{-1}) = 3055, 2985, 2941, 1717, 1497, 1393, 1244, 1129, 1096, 948, 838, 787, 742; MS (ESI), 367 (MH^+), HRMS (ESI, m/z %) calcd. for $C_{18}H_{23}O_8$ [$(M+H)^+$]: 367.1392; found: 367.1398, 1.25 ppm error.

Preparation of methyl-*N*-methyl-2-indole-carboxylate **212**:^(211b)

Methyl iodide (11.4 g, 80 mmol, $\rho = 2.28 \text{ g mL}^{-1}$, 5.0 mL, 18.6 equiv.) was added to a stirred suspension of anhydrous potassium carbonate (6.30 g, 45.6 mmol, 10.1 equiv.) and 1H-indole-2-carboxylic acid **211** (850 mg, 4.3 mmol, 1 equiv.) in anhydrous THF (6 mL) and the mixture was stirred at 80 °C for (3–4) days. Upon cooling to room temperature, the suspension was partitioned between ethyl acetate (75 mL) and water (75 mL). The aqueous layer was extracted with ethyl acetate (2 × 100 mL) and the combined organic layers were dried (MgSO_4), concentrated under reduced pressure to obtain the desired ester as yellow solid (900 mg, 4.76 mmol, 90%). **212**:⁽¹²⁵⁾ m.p. 99–101 °C; $^1\text{H-NMR}$ (400 MHz, CDCl_3 , 25 °C): $\delta = 3.95$ (s, 3H, H_1), 4.12 (s, 3H, H_{11}), 7.19 (t, $J = 7.2$ Hz, 1H, H_9), 7.33 (s, 1H, H_4), 7.37–7.44 (m, 2H, H_7 , H_8), 7.72 (d, $J = 7.8$ Hz, 1H, H_6); $^{13}\text{C-NMR}$: (100 MHz, CDCl_3 , 25 °C): $\delta = 31.5$ (C_{11}), 51.2 (C_1), 110.3 (C_4, C_7), 120.6 (C_9), 122.6 (C_6), 125.0 (C_8), 125.9 (C_3), 127.7 (C_5), 139.7 (C_{10}), 162.7 (C_2); IR (neat): ν_{max} (cm^{-1}) = 3056, 2848, 1662, 1534, 1471, 1395, 1321, 1232, 1155, 1090, 968, 838; MS (ESI), 190 (MH^+), HRMS (ESI, m/z %) calcd. for $\text{C}_{11}\text{H}_{12}\text{NO}_2$ [$(\text{M}+\text{H})^+$]: 190.0868; found: 190.0868, 0 ppm error.

Preparation of 2-(*N*-methyl)indolylmethylacetate **216:** ^(119b)**Procedure A:**

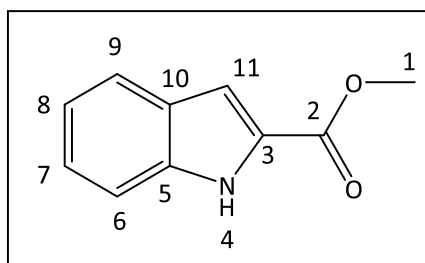
To a solution of 2-hydroxymethyl-1-methyl indole **214** (2 g, 12.40 mmol, 1 equiv.) in acetic anhydride (2.53 g, 24.8 mmol, $p = 1.08 \text{ g mL}^{-1}$, 2.4 mL, 2 equiv.), was added lithium chloride (50 mg, 1.19 mmol, 0.09 equiv.). The resulted solution was stirred at room temperature for 15 hours, after that added diethyl ether (16 mL), washed twice with saturated sodium carbonate solution (8 mL). The aqueous layer was extracted with further diethyl ether ($3 \times 15 \text{ mL}$), and then the extracts combined to dry (MgSO_4). Concentration *in vacuo* afforded the starting material, a white solid, which was used without further purification. No characterisation of **216** was attempted.

Procedure B:

2-Hydroxymethyl-1-methyl indole **214** (1.46 g, 9.05 mmol, 1 equiv.) was dissolved in ether (30 mL), triethylamine (1.09 g, 10.9 mmol, $p = 0.726 \text{ g mL}^{-1}$, 1.5 mL, 1.2 equiv.), 4-(dimethylamino)pyridine (110 mg, 0.9 mmol, 0.1 equiv.) after that acetic anhydride (1.01 g, 9.96 mmol, $p = 1.08 \text{ g mL}^{-1}$, 940 μL , 1.1 equiv.) was added. The resulting mixture was stirred overnight and hydrolysed by the addition of saturated sodium carbonate solution (50 mL). The organic

phase was washed twice with saturated sodium carbonate solution (25 mL), dried (MgSO_4) and concentrated *in vacuo* to obtain a yellow solid (1.54 g, 7.60 mmol, 84%). **216**:⁽¹¹⁹⁾ $R_f = 0.56$ (8:2 hexane/ethyl acetate, det: KMnO_4); m.p. 73-75 °C; $^1\text{H-NMR}$ (400 MHz, CDCl_3 , 25 °C): $\delta = 1.99$ (s, 3H, H_1), 3.55 (s, 3H, H_5), 5.16 (s, 2H, H_3), 6.45 (s, 1H, H_{12}), 6.97-7.01 (m, 1H, H_7), 7.10-7.18 (m, 2H, H_9 , H_{10}), 7.48 (d, $J = 7.8$ Hz, 1H, H_8); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 25 °C): $\delta = 20.9$ (C_1), 29.8 (C_5), 58.2 (C_3), 103.9 (C_{12}), 109.3 (C_{10}), 119.8 (C_7), 121.1 (C_8), 122.4 (C_9), 127.2 (C_{11}), 133.7 (C_6), 138.0 (C_4), 171.5 (C_2); IR (neat): ν_{max} (cm^{-1}) = 3056, 2937, 1729, 1601, 1556, 1436, 1339, 1250, 1146, 1021, 922, 752, 642, 568; MS (ESI), 204 (MH^+), HRMS (ESI, m/z %) calcd. for $\text{C}_{12}\text{H}_{14}\text{NO}_2$ [$(\text{M}+\text{H})^+$]: 204.1024; found: 204.1012, 3.06 ppm error.

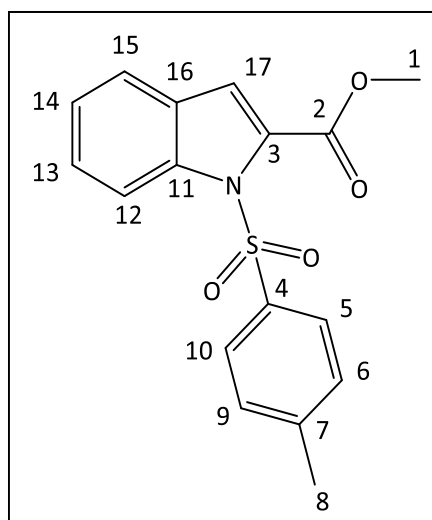
Preparation of methyl-2-indole carboxylate **223**:^(212a)



To a stirred suspension of sodium bicarbonate (3.18 g, 37.8 mmol, 1.5 equiv.) and indole-2-carboxylic acid **212** (3.98 g, 24.7 mmol, 1 equiv.) in anhydrous DMF (20 mL), Methyl iodide (13.68 g, 96.4 mmol, $\rho = 2.28$ g mL^{-1} , 6 mL, 4 equiv.) was added to and the mixture was stirred at room temperature for 3 days. The resulted solution was extracted with further diethyl ether (3×100 mL) and water (50 mL). The extracts were combined, dried (MgSO_4), and concentrated under reduced pressure to obtain the desired ester as yellow

solid (4.0 g, 22.8 mmol, 92%). **223**:^(212b) $R_f = 0.52$ (7:3 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO₄); m.p. 151-152 °C; ¹H-NMR (400 MHz, CDCl₃, 25 °C): $\delta = 3.95$ (s, 3H, H₁), 7.13-7.18 (m, 1H, H₇), 7.22-7.24 (m, 1H, H₁₁), 7.30-7.35 (m, 1H, H₆), 7.42-7.45 (m, 1H, H₉), 7.70 (dt, $J = 8.1, 0.9, 0.9$ Hz, 1H, H₈), 8.85 (br.s, 1H, H₄); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): $\delta = 52.7$ (C1), 108.8 (C11), 111.9 (C6), 120.8 (C8), 122.6 (C9), 125.4 (C6), 127.1 (C3), 127.4 (C10), 136.1 (C5), 162.7 (C2); IR (film): ν_{\max} (cm⁻¹) = 3316, 2952, 1686, 1527, 1439, 1312, 1252, 1209, 773, 747; MS (ESI), 175 (M⁺), HRMS (ESI, m/z %) calcd. for C₁₀H₁₀NO₂ [M⁺]:175.0711; found: 175.0685, 11.46 ppm error.

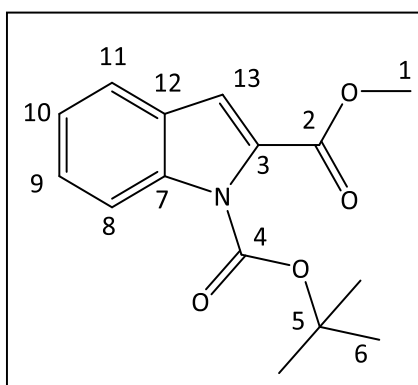
Preparation of methyl *N*-tosyl-2-indole carboxylate **226:**⁽²¹³⁾



To a nitrogen purged round bottom flask containing a solution of sodium hydride (380 mg, 9.57 mmol, 1.3 equiv.) in anhydrous DMF (15 mL), a solution of methyl-2-indole carboxylate **223** (1.29 g, 7.36 mmol, 1 equiv.) in anhydrous DMF (15 mL) was added. The mixture was stirred vigorously for an hour, followed by a solution of *p*-toluenesulfonyl chloride (1.82 g, 9.57 mmol, 1.3 equiv.). The mixture was stirred at room temperature for 24 hours, poured into

water (50 mL), and extracted with further diethyl ether (3 × 50 mL), washed with water (2 × 40 mL), and washed with saturated brine (50 mL). The extract was combined, dried (MgSO₄), and concentrated *in vacuo* to afford the desired ester **226** (790 mg, 2.4 mmol, 33%). **226**: R_f = 0.5 (9.5:0.5 toluene/ethyl acetate, det: KMnO₄); m.p. 82-83 °C; ¹H-NMR (400 MHz, CDCl₃, 25 °C): δ = 2.38 (s, 3H, H₁), 3.94 (s, 3H, H₈), 7.17 (d, *J* = 0.7 Hz, 1H, H₁₂), 7.25-7.26 (m, 1H, H₁₅), 7.27-7.30 (m, 2H, H₆, H₉), 7.44 (ddd, *J* = 8.7, 7.3, 1.2 Hz, 1H, H₁₃), 7.57 (d, *J* = 7.8 Hz, 1H, H₁₄), 7.90-7.93 (m, 2H, H₅, H₁₀), 8.11-8.14 (m, 1H, H₁₇); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 21.6 (C₁), 52.7 (C₈), 115.4 (C₁₇), 116.8 (C₁₂), 122.5 (C₁₄), 124.1 (C₁₅), 127.1 (C₁₃), 127.4 (C_{5,10}), 128.2 (C₃), 129.5 (C_{6,9}), 131.5 (C₁₁), 134.9 (C₁₆), 138.9 (C₇), 145.0 (C₄), 161.7 (C₂); IR (thin film): ν_{max} (cm⁻¹) = 2952, 1734, 1434, 1374, 1341, 1309, 1202, 677, 578; MS (ESI), 330 (MH⁺), HRMS (ESI, *m/z* %) calcd. for C₁₇H₁₆NO₄S [(M+H)⁺]:330.0800; found 330.0807, -0.88 ppm error.

Preparation of methyl *N*-*tert*-butoxycarbonyl-2-indole-carboxylate **224**:



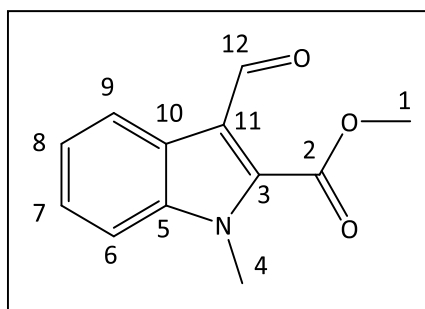
A 100-mL round bottomed flask, the reaction of methyl-2-indole carboxylate **223** (1 g, 5.7 mmol, 1 equiv.) with acetonitrile (70 mL) was fitted with a magnetic stirrer. Subsequently, di-*tert*-butyl dicarbonate (0.14 mg, 1.12 mmol,

0.2 equiv.) was added, immediately turning to red solution. The resulted solution was allowed to heat at 90 °C for 24 hours. At this time, isopropyl amine (344 mg, 5.8 mmol, $\rho = 0.688 \text{ g mL}^{-1}$, 0.5 mL, 1.02 equiv.) was added the solution to remove excess of anhydride. The mixture was stirred further 15 min, and the evaporated *in vacuo* to give a thick oil that dissolved in water (100 mL), extracted with ethyl acetate (150 mL), washed with brine (150 mL), and the dried (MgSO_4) to give the product **224** as yellow solid (1 g, 5.7 mmol, 63%). **214**:⁽²¹⁴⁾ m.p. 62-65 °C; $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): $\delta = 1.55$ (s, 9H, H_6), 3.84 (s, 3H, H_1), 7.03 (s, 1H, H_{13}), 7.16-7.21 (m, 1H, H_8), 7.31-7.34 (m, 1H, H_{11}), 7.52 (dd, $J = 7.9, 0.8 \text{ Hz}$, 1H, H_9), 8.00-8.03 (m, 1H, H_{10}); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3 , 25 °C): $\delta = 27.9$ (C6), 52.4 (C1), 84.7 (C5), 115.0 (13), 122.3 (C8), 123.4 (C10), 126.9 (C9), 127.6 (3), 130.5 (11), 137.9 (C12), 149.3 (C7), 162.5 (C2, C4); IR (KBr): ν_{max} (cm^{-1}) = 3019, 2981, 1745, 1712, 1556; MS (ESI), 298 (MNa^+), HRMS (ESI, m/z %) calcd. for $\text{C}_{15}\text{H}_{17}\text{NNaO}_4$ [$(\text{M}+\text{Na})^+$]:⁽²¹⁴⁾ 298.1050, found 298.1039.

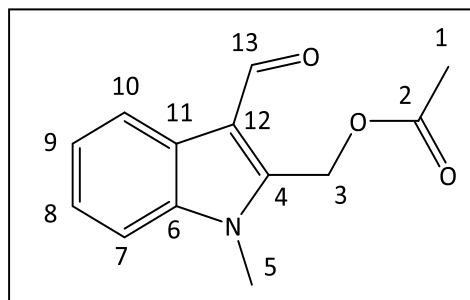
7.2.5 The preparation of 3-formyl indoles *via* Vilsmeier reaction

General procedure 3:

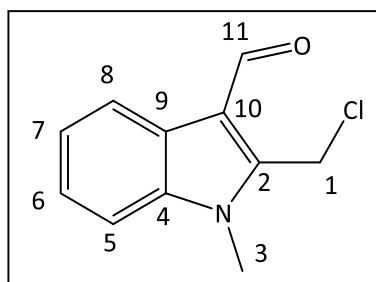
Phosphorus (V) oxychloride [POCl_3] (1.05 equiv.) was added dropwise to cooled ice bath dimethylformamide [DMF] (3.65 equiv.). A solution of *N*-indole derivatives (1 equiv.) in DMF (3 mL) was added and the resulting mixture was stirred at room temperature for 30 min and at 60 °C for 24 h. The reaction mixture was poured into ice (20 mL) and neutralised with 2 M sodium hydroxide. The yellow solid was collected by filtration to give:-

Preparation of methyl 3-formyl-1-methyl-2-indole carboxylate **213**:

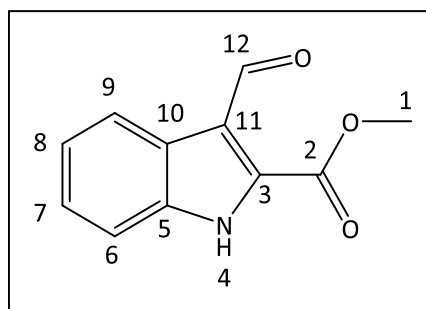
According to **general procedure 3** using methyl-*N*-methyl-2-indole carboxylate **21** (1.0 g, 5.71 mmol, 1 equiv.), POCl₃ (910 mg, 6 mmol, $\rho = 1.645 \text{ g mL}^{-1}$, 550 μL , 1.05 equiv.) and DMF (1.53 g, 21 mmol, $\rho = 0.944 \text{ g mL}^{-1}$, 1.62 mL, 3.65 equiv.) were combined to afford the desired product as yellow solid (610 mg, 2.85 mmol, 50%). **213**:⁽²¹⁵⁾ m.p. 150-151 °C; ¹H-NMR (400 MHz, CDCl₃, 25 °C): δ = 4.09 (s, 3H, H₄), 4.13 (s, 3H, H₁), 7.38-7.42 (m, 1H, H₆), 7.46-7.48 (m, 2H, H₇, H₈), 8.55 (d, $J = 8.1 \text{ Hz}$, 1H, H₉), 10.62 (s, 1H, H₁₂); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 32.4 (C1), 52.7 (C4), 110.2 (C8), 119.0 (C11), 123.0 (C9), 124.1 (C6), 124.6 (C3), 126.5 (C7), 133.1 (C10), 138.3 (C5), 161.5 (C2), 188.3 (C12); IR (KBr): ν_{max} (cm⁻¹) = 1750, 1680; MS (ESI), 218 (MH⁺), HRMS (ESI, m/z %) calcd. for C₁₂H₁₂NO₃ [(M+H)⁺]: 218.0817; found: 218.0813, -0.67 ppm error.

Preparation of *N*-methyl-3-formyl-2-indolylmethylacetate **217**:

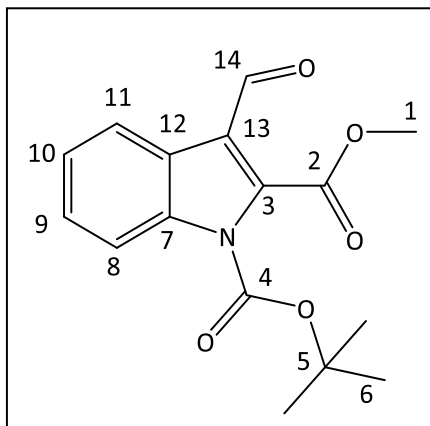
According to **general procedure 3** using 2-(*N*-methyl)indolylmethylacetate **216** (1.55 g, 7.62 mmol, 1 equiv.), POCl₃ (1.22 g, 8 mmol, $\rho = 1.645 \text{ g mL}^{-1}$, 740 μL , 1.05 equiv.) and DMF (2.04 g, 27.9 mmol, $\rho = 0.944 \text{ g mL}^{-1}$, 2.16 mL, 3.65 equiv.) were combined to afford the desired product **217** as yellow solid (960 mg, 4.19 mmol, 55%). **217**: m.p. 127-128.5 °C; ¹H-NMR (400 MHz, CDCl₃, 25 °C): δ = 2.05 (s, 3H, H₁), 3.77 (s, 3H, H₅), 5.51 (s, 3H, H₃), 7.26-7.32 (m, 3H, H₇, H₈, H₉), 8.27 (d, J = 7.6 Hz, 1H, H₁₀), 10.24 (s, 1H, H₁₃); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 20.7 (C₁), 30.3 (C₅), 54.3 (C₃), 109.5 (C₇), 116.0 (C₁₂), 121.8 (C₁₀), 124.4 (C₉), 125.1 (C₈), 123.4 (C₁₁), 137.0 (C₆), 141.3 (C₄), 170.2 (C₂), 184.5 (C₁₃); IR (neat): ν_{max} (cm⁻¹) = 3049, 3019, 2942, 2861, 1743, 1647, 1536, 1473, 1444, 1403, 1335, 1252, 1162, 1049, 978, 911, 767, 753, 728; MS (ESI), 232 (MH⁺), HRMS (ESI, m/z %) calcd. for C₁₃H₁₄NO₃ [(M+H)⁺]: 232.0976; found: 232.0967, 0.45 ppm error.

Preparation of *N*-methyl-3-formyl-2-chloromethyl indole **215**:

According to **general procedure 3** using 2-hydroxymethyl-1-methyl indole **214** (3.00 g, 18.6 mmol, 1 equiv.), POCl₃ (2.99 g, 19.5 mmol, $\rho = 1.645 \text{ g mL}^{-1}$, 1.82 mL, 1.05 equiv.) and DMF (4.99 g, 68.29 mmol, $\rho = 0.944 \text{ g mL}^{-1}$, 2.59 mL, 3.65 equiv.) were combined to afford the product as yellow solid (1.33 g, 7.44 mmol, 40%). **215**: m.p. 122-124 °C; ¹H-NMR (400 MHz, CDCl₃, 25 °C): δ = 3.79 (s, 3H, H₃), 5.05 (s, 2H, H₁), 7.27-7.36 (m, 3H, H₅, H₆, H₇), 8.18 (d, J = 7.8 Hz, 1H, H₈), 10.24 (s, 1H, H₁₁); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 30.0 (C₃), 33.5 (C₁), 108.9 (C₅), 114.5 (C₁₀), 121.0 (C₈), 123.3 (C₇), 124.5 (C₆), 125.6 (C₄), 137.4 (C₉), 142.0 (C₂), 183.8 (C₁₁); IR (neat): ν_{max} (cm⁻¹) = 3028, 1641, 1577, 1476, 1375, 1251, 975, 939, 780, 755, 681, 649; MS (ESI), 208 (MH⁺), HRMS (ESI, m/z %) calcd. for C₁₁H₁₁N³⁵ClO [(M+H)⁺]: 208.0529; found: 208.0525, -0.99 ppm error.

Preparation of methyl-3-formyl-1H-indole-2-carboxylate **229**:⁽²¹⁶⁾

According to **general procedure 3** using methyl-*N*-methyl-2-indole carboxylate **223** (4.1 g, 23.4 mmol, 1 equiv.), POCl₃ (3.76 g, 24.57 mmol, $\rho = 1.645 \text{ g mL}^{-1}$, 2.3 mL, 1.05 equiv.) and DMF (6.25 g, 85.41 mmol, $\rho = 0.944 \text{ g mL}^{-1}$, 6.63 mL, 3.65 equiv.) were combined to afford the desired product as yellow solid (4.05 g, 20.1 mmol, 85%). **229**:⁽²¹⁶⁾ $R_f = 0.56$ (5:5 hexane/ethyl acetate, det: KMnO₄); m.p. 199-201 °C; ¹H-NMR (400 MHz, CDCl₃, 25 °C): $\delta = 4.07$ (s, 3H, H₁), 7.36-7.38 (m, 1H, H₇), 7.42-7.45 (m, 1H, H₈), 7.46-7.49 (m, 1H, H₆), 8.90 (dd, $J = 8.2$, 0.9 Hz, 1H, H₉), 9.39 (br.s, 1H, H₄), 10.75 (s, 1H, H₁₂); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): $\delta = 53.0$ (C1), 111.8 (C6), 115.2 (C7), 119.8 (8), 122.7 (C9), 124.0 (C11), 125.6 (C10), 126.9 (C5), 136.8 (C3), 161.0 (C2), 188.2 (C12); MS (ESI), 204 (MH⁺), HRMS (ESI, m/z %) calcd. for C₁₁H₁₀NO₃ [(M+H)⁺]: 204.0660; found: 204.0656, -0.31 ppm error.

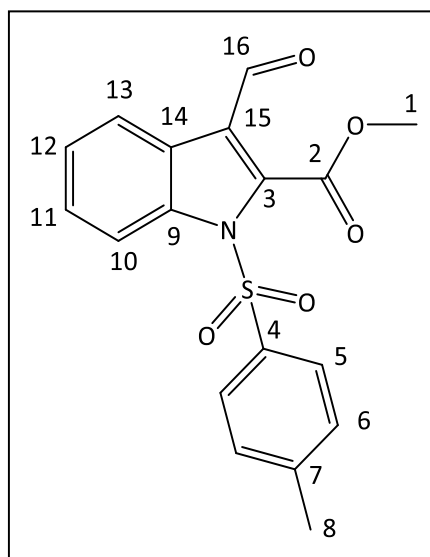
Preparation of methyl-3-formyl-*N*-(tert-butyloxycarbonyl)-2-indolecarboxylate **225**:⁽²¹⁶⁾**Procedure A:**

According to **general procedure 3** using methyl *N*-tert-butoxycarbonyl-2-indole-carboxylate **224** (1.00 g, 3.63 mmol, 1 equiv.), POCl₃ (584 mg, 3.8 mmol, $\rho = 1.645 \text{ g mL}^{-1}$, 350 μL , 1.05 equiv.) and DMF (970 g, 13.2 mmol, $\rho = 0.944 \text{ g mL}^{-1}$, 100 μL , 3.65 equiv.) were combined to afford the **225**, which was used without further purification (800 mg, 2.63 mmol, 73%) as yellow solid. No characterisation of **225** was attempted.

Procedure B:

To a stirred solution of methyl-3-formyl-1H-indole-2-carboxylate **229** (1.2 g, 5.91 mmol, 1 equiv.) in dichloromethane (60 mL), di-*tert*-butyl dicarbonate (1.55 g, 7.10 mmol, 1.2 equiv.), triethylamine (598 mg, 5.91 mmol, $\rho = 0.726 \text{ g mL}^{-1}$, 820 μL , 1 equiv.) and 4-(dimethylamino)pyridine (140 mg, 1.15 mmol, 0.19 equiv.) were added, and the solution was allowed to stir at room temperature for 5 h. After completion of the reaction, the mixture was poured

into saturated sodium bicarbonate (50 mL), extracted with further dichloromethane (2 × 40 mL), and dried (MgSO₄). The resulting residue was purified by column chromatography on silica gel (R_f = 0.53 in 2:8 ethyl acetate/hexane) to give the desired product as yellow solid **225** as yellow solid (1.5 g, 4.9 mmol, 83%). **225**:⁽²¹⁷⁾ R_f = 0.53 (SiO₂, 8:2 hexane/ethyl acetate, det: KMnO₄); m.p. 70-73 °C; ¹H-NMR (400 MHz, CDCl₃, 25 °C): δ = 1.67 (s, 3H, H₆), 4.04 (s, 3H, H₁), 7.42 (dd, *J* = 7.8, 1.0 Hz, 1H, H₁₁), 7.47 (dd, *J* = 8.4, 1.3 Hz, 3H, H₉), 8.10 (d, *J* = 8.6 Hz, 1H, H₈), 8.35 (d, *J* = 8.2 Hz, 1H, H₁₀), 10.21 (s, 1H, H₁₄); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 27.9 (C₆), 53.249 (C₁), 86.7 (C₅), 114.9 (C₈), 121.0 (C₁₃), 122.9 (C₁₀), 124.8 (C₃), 125.2 (C₁₁), 135.8 (C₁₂), 137.6 (C₇), 148.3 (C₄), 161.6 (C₂), 186.0 (C₁₄); IR (KBr): ν_{max} (cm⁻¹) = 3445, 3007, 2973, 2869, 1750, 1729, 1666, 1559, 1436, 1396, 1237, 1111, 748, 695; MS (ESI), 304 (MH⁺), HRMS (ESI, m/z %) calcd. for C₁₆H₁₈NO₅ [(M+H)⁺]: 304.1184; found: 304.1188, -1.51 ppm error.

Preparation of methyl-3-formyl-*N*-Ts-2-indole carboxylate 227:**Procedure A:**

According to **general procedure 7** using of methyl *N*-Ts-indole-2-carboxylate **226** (330 mg, 1.00 mmol, 1 equiv.), POCl₃ (160 mg, 1.05 mmol, $\rho = 1.645 \text{ g mL}^{-1}$, 100 μL , 1.05 equiv.) and DMF (267 mg, 3.65 mmol, $\rho = 0.944 \text{ g mL}^{-1}$, 280 μL , 3.65 equiv.) were combined to afford the desired product as yellow solid (99 mg, 0.27 mmol, 20%). **227**: $R_f = 0.53$ (9:1 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO₄).

Procedure B:

To a stirred solution of sodium hydride (58 mg, 1.48 mmol, 1.2 equiv.) in anhydrous DMF (1 mL) at 0 °C was added a solution of methyl-3-formyl-1H-indole-2-carboxylate **229** (250 mg, 1.23 mmol, 1 equiv.) in anhydrous DMF (1 mL) with stirring for 30 min., and then a solution of tosyl chloride (468 mg, 2.46 mmol, 2 equiv.) was added to the previous mixture. The resulting solution was

allowed to stir at room temperature for 24 hours, poured into water (50 mL), extracted with further ethyl acetate (3 × 50 mL), washed with water (50 mL), saturated brine (50 mL), and dried (MgSO₄). Purification of the residue *via* flash chromatography on silica using 70:30 petroleum ether (b.p. 40-60 °C)/ethyl acetate as the eluent afforded the desired product **227** (130 mg, 0.36 mmol, 30%). **227**: R_f = 0.50 (7:3 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO₄).

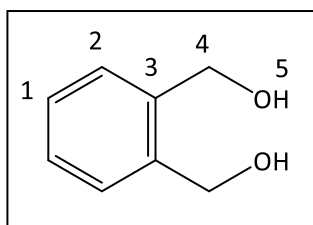
Procedure C:^(115b)

A solution of dichloromethyl methyl ether (114 mg, 2.26 mmol, $\rho = 1.271 \text{ g mL}^{-1}$, 200 μL , 3 equiv.) in (1.5 mL) of anhydrous dichloromethane was added dropwise to a cooled (-78 °C) solution of methyl *N*-tosyl-indole-2-carboxylate **226** (250 mg, 0.76 mmol, 1 equiv.) and silver triflate (585 mg, 2.28 mmol, 3 equiv.) in anhydrous dichloromethane (10 mL). The resulted solution was stirred at -78 °C for 10 min, added saturated sodium bicarbonate solution (40 mL), and then stirred further 30 min at 0°C. The mixture was filtered through a pad of celite, extracted with ethyl acetate (2x 50 mL), washed with brine (50 mL) and dried (MgSO₄). Purification of the residue *via* flash chromatography on silica using 80:20 hexane/ethyl acetate as the eluent afforded the desired product **227** (250 mg, 0.7 mmol, 92%). **227**: R_f = 0.43 (8:2 hexane/ethyl acetate, det: KMnO₄); m.p. 120-122 °C; ¹H-NMR (300 MHz, CDCl₃, 25 °C): δ = 2.38 (s, 3H, H₈), 4.11 (s, 3H, H₁), 7.29-7.32 (m, 2H, H₆), 7.35-7.40 (m, 1H, H₁₂), 7.43-7.49 (m, 1H, H₁₀), 7.97 (d, J = 8.5 Hz, 2H, H₅), 8.01 (d, J = 8.3 Hz, 1H, H₁₁), 8.26-8.29 (m, 1H, H₁₃), 10.13 (s, 1H, H₁₆); ¹³C-NMR (75 MHz, CDCl₃, 25 °C): δ =

21.8 (C8), 54.008 (C1), 114.1 (C10), 121.0 (C15), 123.0 (C13), 125.1 (C11), 127.4 (C5), 127.7 (C6), 130.2 (C14), 134.1 (C9), 135.2 (C4), 138.6 (C7), 146.4 (C3), 161.5 (C2), 185.2 (C16); IR (neat): ν_{\max} (cm^{-1}) = 2952, 2852, 2764, 1724, 1676, 1434, 1370, 1339, 1325, 1140, 1086, 960, 717, 666, 569; MS (ESI), 358 (MH^+), HRMS (ESI, m/z %) calcd. for $\text{C}_{18}\text{H}_{16}\text{NO}_5\text{S}$ [$(\text{M}+\text{H})^+$]: 358.0749; found: 358.0746, -1.02 ppm error.

7.2.6 Preparation of diols

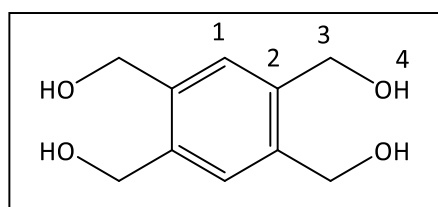
Preparation of benzene-1,2-dimethanol **202**:



A solution of phthalaldehyde **208** (200 mg, 1.49 mmol, 1 equiv.) in methanol (50 mL) was cooled to (0–5 °C) and then sodium tetrahydroborate added (846 mg, 2.24 mmol, 1.5 equiv.) slowly. After 30 min, the reaction was acidified with glacial acetic acid (1 mL), and the solution was stirred for 10 min and then evaporated to a small amount. The residue was suspended in saturated sodium bicarbonate (100 mL) and the mixture extracted with dichloromethane (3 × 100 mL). The organic layer was dried (MgSO_4), and evaporated to dryness *in vacuo* to afford white solid (660 mg, 4.77 mmol, 33%). **202**:^(113a) m.p. 62–65 °C; ^1H -NMR (300 MHz, CDCl_3 , 25 °C) δ = 3.07 (s, 2H, H_5), 4.76 (s, 4H, H_4), 7.33–7.39 (m, 4H, H_1 , H_2); ^{13}C -NMR (75 MHz, CDCl_3 , 25 °C) δ = 64.1 (C4), 128.5 (C1), 129.7 (C2), 139.4 (C3); IR (neat): ν_{\max} (cm^{-1}) = 3325, 2878, 1619, 1453, 1366, 1290, 1219, 1184, 1106, 998, 911, 733; GC-MS (EI, 70 eV): m/z (%) = 120 (100),

91 (83), 77 (29), 65 (16), 51 (9), 39 (7), 29 (3); MS (ESI), 139 (MH⁺), HRMS (ESI, m/z %) calcd. for C₈H₁₀O₂ [(M+H)⁺]: 139.0759; found: 139.0572, 3.85 ppm error.

Preparation of 1,2,4,5- tetrakis(hydroxymethyl) benzene **203:** ⁽¹¹⁵⁾



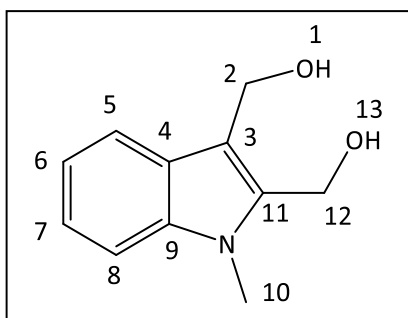
To a cooled (0 °C) suspension of Lithium aluminum hydride (1.24 g, 32.7 mmol, 6 equiv.) in anhydrous THF (50 mL) under nitrogen pressure, a solution of tetraethyl pyromellitate **210** (2.00 g, 5.45 mmol, 1.5 equiv.) in anhydrous THF (50 mL) was added slowly. The reaction mixture was stirred at room temperature for 24 h. Then the mixture was acidified with 10% sulfuric acid. The solid formed was removed by filtration and heated to reflux in pyridine (20 mL) for an hour then filtered. The crude was evaporated to a small volume. Addition of hexane (30 mL) precipitated a white solid (330 mg, 1.66 mmol, 50%) which collected by filtration. **203**: m.p. 189-191 °C; ¹H-NMR (300 MHz, D₆-DMSO, 25 °C): δ = 4.50 (s, 8H, H₃), 7.40 (s, 2H, H₁); ¹³C- NMR (75 MHz, D₆-DMSO, 25 °C): δ = 61.0 (C3), 126.2 (C2), 147.0 (C1); IR (neat): ν_{max} (cm⁻¹) = 3189, 2888, 1636, 1466, 1305, 1211, 1185, 1132, 1049, 993, 818, 758, 657; MS (ESI), 198 (MH⁺), HRMS (ESI, m/z %) calcd. for C₁₀H₁₅O₄ [(M+H)⁺]: 198.0970; found: 199.0953, 11.39 ppm error.

7.2.7 The reduction of indole derivatives

General procedure 4:

To a solution of the indole derivative (1 equiv.) in anhydrous THF (20 mL) cooled to -10 °C was added lithium aluminum hydride (5.3 equiv.) after that the solution was stirred for the time stated. The unreacted lithium aluminum hydride was quenched by gradually adding ethyl acetate (20 mL) followed by water (17 mL). The organic layer was separated and the aqueous layer extracted again with ethyl acetate (50 mL). The combined extracts were dried (MgSO₄) and concentrated to obtain diols.

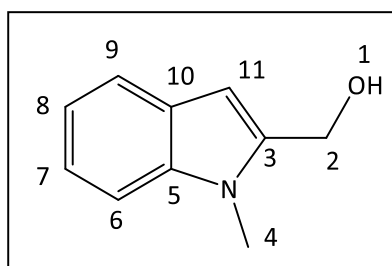
Preparation of *N*-methyl-2, 3-dimethanol indole **205**:



According to **general procedure 4** using methyl-3-formyl-1-methyl-2-indole carboxylate **213** (1.62 g, 7.45 mmol, 1 equiv.) and lithium aluminum hydride (1.49 g, 39.5 mmol, 5.3 equiv.) were combined to afford the desired product as yellow solid (570 mg, 2.98 mmol, 40%). **205**: m.p. 99-100 °C; ¹H-NMR (400 MHz, CDCl₃, 25 °C): δ = 1.98 (s, 1H, H₁), 2.6 (s, 1H, H₁₃), 3.78 (s, 3H, H₁₀), 4.82 (s, 2H, H₂), 4.87 (s, 2H, H₁₂), 7.16 (d, *J* = 7.6 Hz, 1H, H₆), 7.20-7.23 (m, 1H, H₈), 7.30-7.32 (m, 1H, H₇), 7.66 (d, *J* = 7.8 Hz, 1H, H₅); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 29.8 (C₁₀), 54.4 (C₁₂), 55.46 (C₂), 108.9 (C₈), 112.9 (C₃), 118.7 (C₅), 119.9

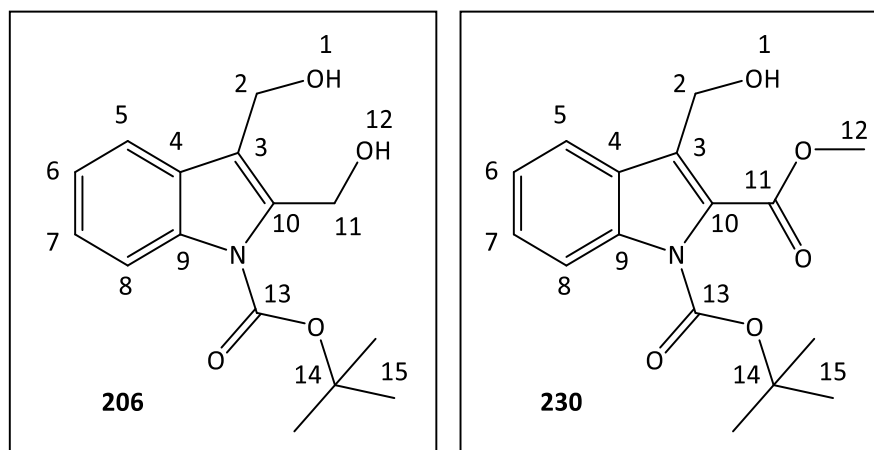
(C6), 122.5 (C7), 126.4 (C4), 128.6 (C9), 137.1 (C11); IR (neat): ν_{\max} (cm⁻¹) = 3280, 2971, 2877, 1451, 1381, 1094, 1056, 1005, 885, 776, 750, 680, 636; MS (ESI), 192 (MH⁺), HRMS (ESI, m/z %) calcd. for C₁₁H₁₄O₂ [(M+H)⁺]: 192.1024; found: 192.1020, – 0.04 ppm error.

Preparation of 2-hydroxymethyl-1-methyl indole **214:**⁽¹¹⁹⁾



According to **general procedure 4** using methyl-*N*-methyl-2-indole carboxylate **212** (2.85 g, 15.1 mmol, 1 equiv.) and lithium aluminum hydride (3.03 g, 79.8 mmol, 5.3 equiv.) were combined to afford the desired product as yellow solid (2.20 g, 13.6 mmol, 90%). **214**:⁽²¹⁸⁾ m.p. 100-101 °C; ¹H-NMR (400 MHz, CDCl₃, 25 °C): δ = 3.74 (s, 3H, H₄), 4.74 (s, 2H, H₂), 6.39 (s, 1H, H₁₁), 7.01-7.05 (m, 1H, H₈), 7.14-7.18 (m, 1H, H₆), 7.24-7.26 (m, 1H, H₇), 7.52 (d, *J* = 7.3 Hz, 1H, H₉); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 29.8 (C3), 57.6 (C2), 101.4 (C11), 109.2 (C6), 119.6 (C7), 120.8 (C8), 122.0 (C9), 127.2 (C10), 138.2 (C5), 138.7 (C3); IR (neat): ν_{\max} (cm⁻¹) = 3515, 3053, 2873, 1701, 1612, 1548, 1431, 1365, 1217, 1137, 1008, 962, 778; MS (ESI), 162 (MH⁺), HRMS (ESI, m/z %) calcd. for C₁₀H₁₂NO [(M+H)⁺]: 162.0918; found: 162.0915, –0.62 ppm error.

Preparation of *N*-(*tert*-butoxycarbonyl)- 2,3-bis(hydroxymethyl)-indole (206) and 1-(*tert*-butyl) 2-methyl 3-(hydroxymethyl)-1*H*-indole-1,2-dicarboxylate (230):



Procedure A:

According to **general procedure 4** using methyl 3-formyl-1-(*tert*-butoxycarbonyl)-1*H*-indole-2-carboxylate **225** (1.00 g, 3.29 mmol, 1 equiv.) and lithium aluminum hydride (624 g, 16.45 mmol, 5.3 equiv.) were combined to afford the desired product as white solid (50 mg, 0.18 mmol, 5.5%). **206**: R_f = 0.5 (5:5 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO_4). Additionally, unexpected product **230** was found as white solid (180 mg, 0.59 mmol). The product **230** (180 mg, 0.59 mmol, 1 equiv.) was reacted again according to **general procedure 6** with lithium aluminum hydride (118 mg, 3.13 mmol, 5.3 equiv.) to afford the desired product **225** as white solid (10 mg, 0.036 mmol, 6.13%). **225**: R_f = 0.5 (1.5:8.5 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO_4).

Procedure B:

Using the same **general procedure 4** using methyl 3-formyl-1-(*tert*-butyloxycarbonyl)-1H-indole-2-carboxylate **225** (1.00 g, 3.29 mmol, 1 equiv.) and lithium aluminum hydride (624 g, 16.45 mmol, 5.3 equiv.) were combined. The resulted solution after adding a solution of indole in anhydrous THF, was heated at 70°C for 24 h, followed by doing its workup to afford the desired product as white solid (100 mg, 0.36 mmol, 11%). **206**: R_f = 0.5 (2:8 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det:KMnO₄).

Procedure C:

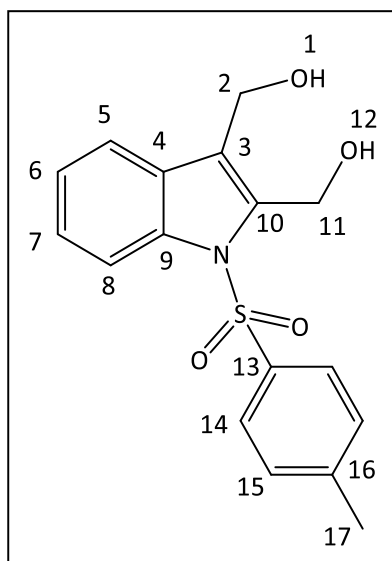
To a cooled solution of diisobutylaluminum hydrid (1.0 M in Toluene, 1.08 mL, 6.55 mmol, 4 equiv.) in dichloromethane (7 mL), was added slowly a solution of methyl 3-formyl-1-(*tert*-butyloxycarbonyl)-1H-indole-2-carboxylate **225** (500 mg, 1.63 mmol, 1 equiv.) in anhydrous THF (7 mL). The resulted solution was stirred at room temperture for 3-5 h, followed by adding methanol (70 mL). This solution was cooled at 0 °C then 2 N hydrochoric acid (5 mL) was added. The solution was further stirred for 1 h, separated the organic layer. Concentration *in vacuo* afforded the starting material. No characterisation of **206** was attempted by this methodolgy.

Procedure D:

Lithium borohydride (570 mg, 26.4 mmol, 4 equiv.) was added in a three portions to a solution of methyl 3-formyl-1-(*tert*-butyloxycarbonyl)-1H-indole-2-carboxylate **225** (2.0 g, 6.6 mmol, 1 equiv.) in anhydrous THF (80 mL). The

mixture was stirred vigorously for 22 h at room temperature under a N₂ atmosphere. The mixture was cooled at 0 °C then saturated ammonium chloride (15 mL) was added, and then extracted with ethyl acetate (2 × 100 mL). The combined ethyl acetate extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to afford the crude product. Purification *via* flash chromatography on silica gel using 8:2 petroleum ether (b.p. 40-60 °C)/ethyl acetate as the eluent afforded **206** as a yellow solid (820 mg, 2.94 mmol, 46%).

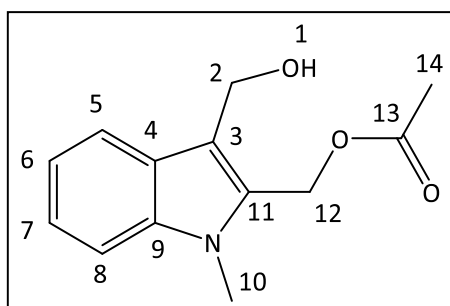
206: R_f = 0.56 (8:2 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO₄); m.p. 111-113 °C; ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 1.75 (s, 9H, H₁₅), 2.10 (br.s, 1H, H₁₂), 3.99 (s, 1H, H₁), 4.85 (s, 2H, H₂), 4.90 (s, 2H, H₁₁), 7.27-7.33 (m, 2H, H₆, H₇), 7.70-7.73 (m, 1H, H₅), 8.00 (dd, *J* = 15.2, 7.6 Hz, 1H, H₈); ¹³C-NMR (100 MHz, CDCl₃, 25 °C) δ = 28.3 (C₁₅), 55.1 (C₂), 55.2 (C₁₁), 115.7 (C₈), 119.5 (C₅), 120.6 (C₁₄), 123.2 (C₆), 125.1 (C₇), 128.8 (C₃), 135.4 (C₄), 136.6 (C₁₀), 151.5 (C₁₃); IR (neat): ν_{max} (cm⁻¹) = 3504, 2990, 2951, 1702, 1577, 1478, 1386, 1258, 1156, 1118, 1034, 1007, 985, 933, 771, 749, 535; MS(ESI), 300 (MNa⁺), HRMS (ESI, *m/z* %) Calcd for C₁₅H₁₉NNaO₄ [(M+Na)⁺] 300.1211; found 300.1179, 9.6 ppm.

Preparation of *N*-(toluene-4-sulfonyl)-2,3-bis(hydroxymethyl) indole **207**:

To a stirred solution of 3-formyl-methyl *N*-tosylindole-2-carboxylate **227** (300 mg, 0.84 mmol, 1 equiv.) in anhydrous THF (20 mL) at room temperature under a N₂ atmosphere was added lithium borohydride (73 mg, 3.36 mmol, 4 equiv.) in portions. The resultant solution was stirred for 24 h after which time the mixture had cooled, saturated ammonium chloride (12 mL), extracting with ethyl acetate (2 × 50 mL). The extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified *via* flash chromatography on silica gel using 9.5:0.5 dichloromethane/methanol as the eluent gave the title diol **207** as a white solid (200 mg, 0.60 mmol, 71%). **207**: m.p. 173-175 °C; R_f = 0.16 (9.5:0.5 dichloromethane/ methanol, det: KMnO₄); ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 1.61 (s, 2H, H₁, H₁₂), 2.34 (s, 3H, H₁₇), 4.84 (s, 2H, H₁₁), 4.98 (s, 2H, H₂), 7.20 (d, *J* = 7.3 Hz, 2H, H₁₅, H₁₈), 7.29 (d, *J* = 7.5 Hz, 1H, H₆), 7.34 (d, *J* = 7.3 Hz, 1H, H₇), 7.65 (d, *J* = 7.3 Hz, 1H, H₅), 7.74 (d, *J* = 7.0 Hz, 2H, H₁₄, H₁₉), 8.11 (d, *J* = 7.8 Hz, 1H, H₈); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 21.6 (C₁₇), 55.0 (C₁₁), 55.3 (C₂), 114.6 (C₈), 119.8 (C₅), 122.0 (C₃), 123.9 (C₆), 125.7 (C₇), 128.5

(C10), 128.9 (C14, C19), 130.0 (C15, C18), 135.7 (C16), 136.2 (C4), 137.1 (C9), 145.3 (C13); IR (neat): ν_{max} (cm^{-1}) = 3669, 2970, 2901, 1557, 1453, 1393, 151, 1165, 1033, 980; MS (ESI), 354 (MNa^+), HRMS (ESI, m/z %) Calcd for $\text{C}_{17}\text{H}_{17}\text{NNaO}_4\text{S}$ [$(\text{M}+\text{Na})^+$] 354.0776; found 354.0749, 5.77 ppm error.

Preparation of *N*-methyl-3-methanol-2-indolylmethylacetate **219:**



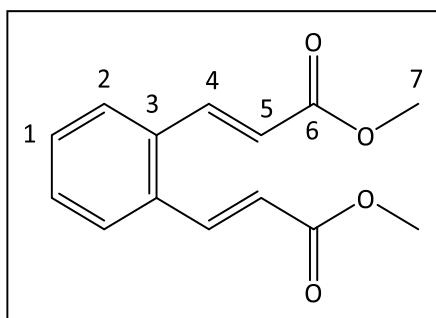
A solution of *N*-methyl-3-formyl-2-indolylmethylacetate **217** (750 mg, 3.24 mmol, 1 equiv.) in methanol (50 mL) was cooled to (0-5 °C) and then sodium borohydride was added (180 mg, 4.86 mmol, 2 equiv.) slowly. After 30 min, the reaction was acidified with glacial acetic acid (2 mL), and the solution was stirred for 10 min and then evaporated to a small amount. The residue was suspended in saturated sodium bicarbonate solution (100 mL) and the mixture extracted with dichloromethane (100 mL). The organic layer was dried (MgSO_4), and evaporated to dryness *in vacuo* to afford white solid, which was used without further purification (700 mg, 3.00 mmol, 93%). No characterisation of **219** was attempted (no reaction).

7.2.8 Preparation of trienes *via* TOP reaction:

General procedure 5:

Activated manganese dioxide (10 equiv.) was added to a stirred solution of diol (1 equiv.) and ylide (2.5-5 equiv.) in anhydrous THF (20 mL). The resulting solution was stirred and heated to reflux for 24 h. The manganese dioxide was removed by filtration through a celite pad, washed with THF (50 mL) and then concentrated under higher vacuum. The crudes were purified by column chromatography to give the desired trienes. Conversion was determined by analysis of the ^1H -NMR spectrum.

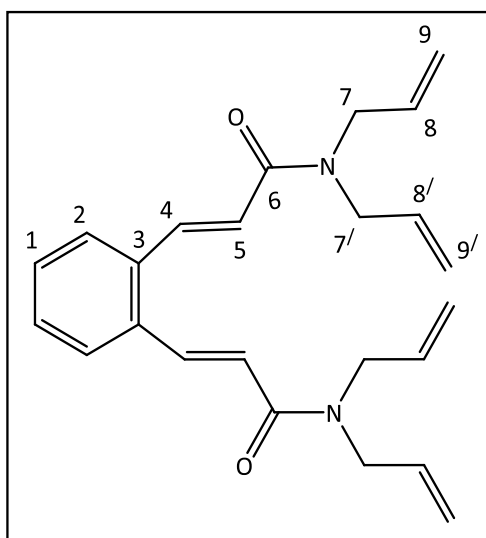
Preparation of (2*E*,2'*E*)-dimethyl-3,3'-(1,2-phenylen)diacrylate **256**:



According to **general procedure 5** using benzene-1,2-dimethanol **202** (200 mg, 1.45 mmol, 1 equiv.), manganese dioxide (1.25 g, 14.5 mmol, 10 equiv.) and methyl (triphenylphosphoranylidene) acetate **52** (1.20 g, 3.62 mmol, 2.5 equiv.) were combined to afford the desired product as white solid (175 mg, 0.71 mmol, 50%). **256**:⁽²¹⁹⁾ R_f = 0.54 (7:3 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO_4); m.p. 71-73 °C; ^1H -NMR (300 MHz, CDCl_3 , 25 °C): δ = 3.78 (s, 6H, H_7), 6.33 (d, J = 15.8 Hz, 2H, H_5), 7.37 (m, 2H, H_1), 7.54 (m, 2H, H_2), 8.01 (d, J = 15.8 Hz, 2H, H_4); ^{13}C -NMR (75 MHz, CDCl_3 , 25 °C): δ = 51.7 (C7), 121.6

(C5), 127.6 (C1), 130.1 (C2), 134.3 (C3), 141.5 (C4), 166.8 (C6); IR(neat): ν_{\max} (cm⁻¹) = 2951, 1712, 1312, 1168, 975; MS (ESI), 246 (MH⁺), HRMS (ESI+ m/z%): calcd for C₁₄H₁₅O₄ [(M+H)⁺]: 246.0970, found 246.0976, -3.95 ppm error.

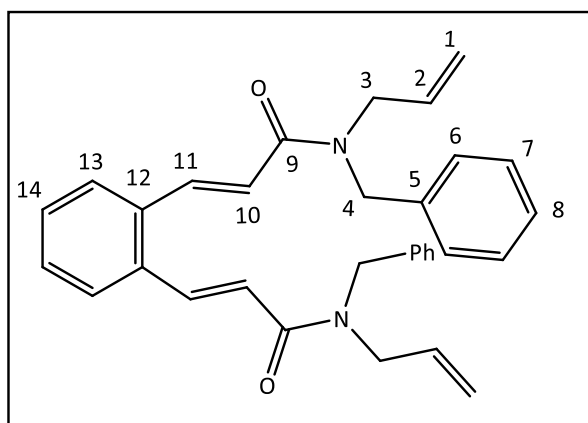
Preparation of (*E*)-3-{*o*-[(*E*)-3-(diallylamino)-3-oxo-1-propenyl]-phenyl}-1-(diallylamino)-2-propen-1-one **257:**



According to **general procedure 5** using benzene-1,2-dimethanol **202** (200 mg, 1.45 mmol, 1 equiv.), manganese dioxide (1.25 g, 14.5 mmol, 10 equiv.) and *N,N*-diallyl (triphenylphosphoranylidene) acetamide **252** (1.48 g, 3.6 mmol, 2.5 equiv.) were combined to afford the desired product as white solid (220 mg, 0.57 mmol, 40%). **257**: m.p. 150-151 °C; R_f = 0.39 (5:5 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO₄); ¹H-NMR (400 MHz, CDCl₃, 25 °C): δ = 4.03-4.05 (m, 2H, H₇), 4.09 (d, J = 6.0 Hz, 2H, H₇), 5.17 (s, 2H, H₉), 5.22 (s, 2H, H_{9'}), 5.83-5.87 (m, 2H, H₈), 6.61 (d, J = 15.7 Hz, 1H, H₅), 7.35 (dd, J = 5.7, 3.2 Hz, 1H, H₂), 7.44-7.49 (m, 1H, H₁), 7.98 (d, J = 14.9 Hz, 1H, H₄); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 48.3 (C7), 49.8 (C3'), 116.7 (C9), 117.5 (C9'), 122.1 (C5), 128.4 (C1), 129.4 (C2), 133.3 (C8), 135.4 (C3), 140.7 (C4), 169.2 (C6); IR (neat): ν_{\max}

(cm^{-1}) = 3073, 2979, 2925, 1649, 1639, 1604, 1458, 1032, 998, 954, 929, 775, 731; MS (ESI), 377 (MH^+), HRMS (ESI+ m/z): calcd for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_2$ [$(\text{M}+\text{H})^+$]: 377.2229, found 377.2244, -4.47 ppm error.

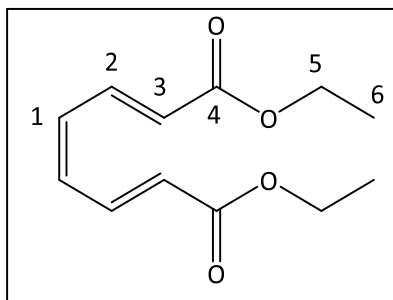
Preparation of (*E*)-3-(*o*-{(*E*)-3-[(benzyl)-*N*-allylamino]-3-oxo-1-propenyl}phenyl)-1-[(benzyl)-*N*-allyl-amino]-2-propen-1-one **258:**



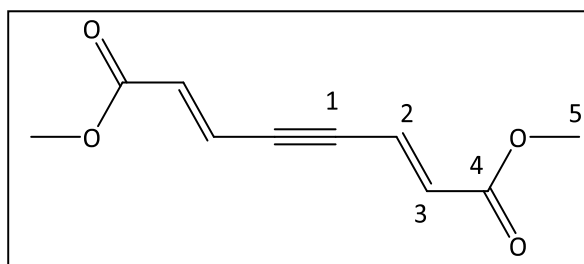
According to **general procedure 5** using benzene-1,2-dimethanol **202** (500 mg, 3.62 mmol, 1 equiv.), manganese dioxide (3.15 g, 36.2 mmol, 10 equiv.) and *N*-allyl-*N*-benzyl (triphenylphosphoranylidene) acetamide **253** (3.62 g, 9.05 mmol, 2.5 equiv.) were combined. NMR of the mixture following chromatography showed an inseparable mixture of the intermediate dialdehyde (phthaldialdehyde) to the desired product in an $\sim 4:1$ ratio. No further purification was attempted. **258**: $R_f = 0.39$ (5:5 petroleum ether (b.p. 40-60 $^{\circ}\text{C}$)/ethyl acetate, det: KMnO_4); ^1H -NMR (300 MHz, CDCl_3 , selected signals only, 25 $^{\circ}\text{C}$), NMR showed the presence of a 55:45 mixture of rotamers: $\delta = 3.99$ -4.01 (m, 2H, H_7 major), 4.10-4.13 (m, 2H, H_7 minor), 4.68 (s, 2H, H_{10} minor), 4.70 (s, 2H, H_{10} major), 5.10-5.30 (m, 4H, H_{9a} major, H_{9a} minor, H_{9b} major, H_{9b} minor), 5.75-5.90 (m, 2H, H_{8a} major, H_{8a} minor), 6.75 (d, $J = 15.2$ Hz, 2H, H_5 minor, H_5 major), 8.48 (d, $J =$

15.2 Hz, 2H, H₄ minor, H₄ major); MS (ESI), 477 (MH⁺), HRMS (ESI, m/z %) calcd. for C₃₂H₃₃N₂O₂ [M + H⁺]: 477.2542; found: 477.2536, 0.19 ppm error.

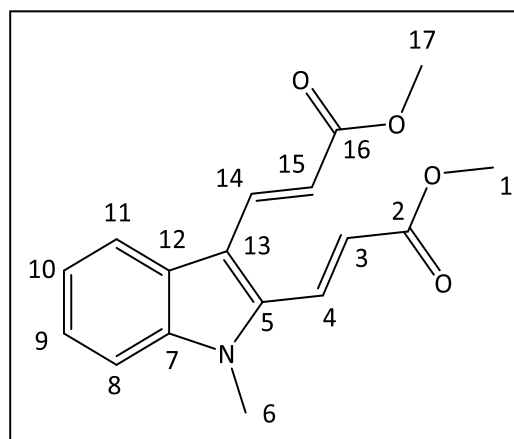
Preparation of dimethyl-2,4,6-octatrienedioate **261**:



According to **general procedure 5** using (Z)-2-butene-1,4-diol **260** (200 mg, 2.26 mmol, $p = 1.072 \text{ g mL}^{-1}$, 180 μL , 1 equiv.), manganese dioxide (1.96 g, 22.6 mmol, 10 equiv.) and methyl (triphenylphosphoranylidene)acetate **52** (1.89 g, 5.65 mmol, 2.5 equiv.) were combined to afford the desired product as yellow solid (400 mg, 2.04 mmol, 90%). **261**:⁽²²⁰⁾ m.p. 112-116 °C; $R_f = 0.50$ (9.5:0.5 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO₄); ¹H-NMR (300 MHz, CD₃OD, 25 °C), NMR showed the presence of a 3:1 mixture of (2E,4E,6E: 2E,4Z,6E) isomers: $\delta = 3.78$ (s, 3H, H₅ EZE), 3.81 (s, 3H, H₅ EEE), 6.01 (d, $J = 15.2$ Hz, 2H, H₃EEE), 6.03 (d, $J = 15.2$ Hz, 2H, H₃EZE), 6.40 (dd, $J = 8.6, 2.3$ Hz, 2H, H₁ EEE), 6.62 (dd, $J = 7.5, 3.2$ Hz, 2H, H₁ EZE), 7.32 (ddd, $J = 15.2, 7.5, 3.2$ Hz, 2H, H₂ EZE), 7.81 (ddd, $J = 15.2, 8.6, 2.3$ Hz, 2H, H₂ EEE); ¹³C-NMR (75 MHz, CD₃OD, 25 °C): $\delta = 50.9$ (C5), 124.2 (C1), 133.4 (C3), 137.7 (C2), 167.2 (C4); IR (KBr): ν_{max} (cm⁻¹) = 2919, 2850, 1708, 1624, 1464, 1367, 1318, 1270, 1164, 1025, 982, 727; MS (ESI), 197 (MH⁺), HRMS (ESI, m/z %) calcd. for C₁₀H₁₃O₄ [(M+H)⁺]: 197.0813; found: 197.0806, 1.70 ppm error.

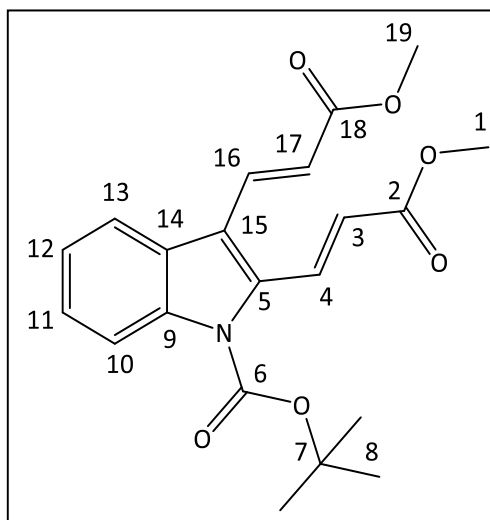
Preparation of dimethyl (2*E*,6*E*)-2,6-octadien-4-ynedioate **263**:

According to **general procedure 5** using 2-butyne-1,4-diol **262** (200 mg, 2.32 mmol, 1 equiv.), manganese dioxide (200 mg, 23.2 mmol, 10 equiv.) and methyl (triphenylphosphoranylidene)acetate **52** (1.9 g, 5.8 mmol, 2.5 equiv.) were combined to afford the desired product as white solid (60 mg, 0.3 mmol, 13%). **263**:⁽²⁰⁵⁾ R_f = 0.54 (9:1 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO_4); m.p. 106-110 °C; $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): δ = 3.72 (s, 3H, H_5), 6.25 (d, 2H, J = 14.9 Hz, H_3), 6.83 (d, J = 16.1 Hz, 2H, H_2); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3 , 25 °C): δ = 53.6 (C5), 68.0 (C1), 128.6 (C3), 132.0 (C2), 157.7 (C4); IR (KBr): ν_{max} (cm^{-1}) = 2924, 2853, 2200, 1715, 1610, 1467, 1317, 1273, 1167, 978.

Preparation of dimethyl 3,3'-(1-methyl-1H-indole-2,3-diyl)diacrylate **267**:

According to **general procedure 5** using *N*-methyl-2,3-dimethanol indole **205** (990 mg, 5.17 mmol, 1 equiv.), manganese dioxide (4.49 g, 51.7 mmol, 10 equiv.) and methyl (triphenylphosphoranylidene)acetate **52** (8.64 g, 25.85 mmol, 5 equiv.) were combined to afford the desired product as yellow oil (300 mg, 1.00 mmol, 19%). **267**:⁽²²¹⁾ R_f = 0.50 (7:3 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO_4); $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): δ = 3.75 (s, 3H, H_1), 3.76 (s, 3H, H_{17}), 3.79 (s, 3H, H_6), 6.25 (d, J = 16 Hz, 1H, H_3), 6.50 (d, J = 16 Hz, 1H, H_{15}), 7.16-7.22 (m, 2H, H_8 , H_9), 7.29-7.30 (m, 2H, H_{10} , H_{11}), 7.82 (d, J = 16 Hz, 1H, H_{14}), 7.93 (d, J = 16 Hz, 1H, H_4); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3 , 25 °C): δ = 31.3 (C6), 51.6 (C1), 52.1 (C17), 110.1 (C), 114.1 (CH), 116.2 (CH), 121.1 (CH), 122.7 (CH), 124.1 (CH), 124.7 (C), 125.4 (CH), 131.3 (CH), 136.8 (C), 139.0 (C), 143.2 (CH), 166.5 (C2), 168.3 (C16); IR (KBr): ν_{max} (cm^{-1}) = 2948, 2841, 1702, 1618, 1433, 1410, 1372, 1341, 1269, 1190, 1165, 1132, 1035, 1013, 967, 739, 648, 560; GC-MS (EI, 70 eV): m/z (%) = 299 (M^+ , 60), 240 (67), 209 (64), 181 (100), 120 (32), 77 (19), 41 (19).

Preparation of dimethyl 3,3'-(*N*-(*tert*-butoxycarbonyl)-1*H*-indole-2,3-diyl)diacrylate **268**:

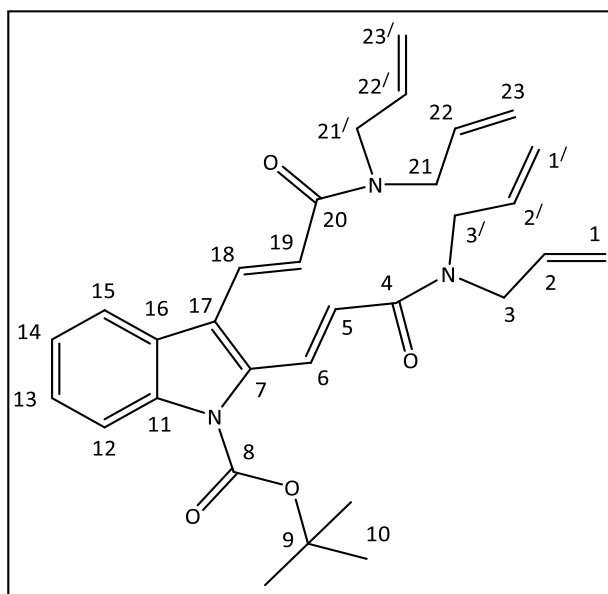


According to **general procedure 5** using *N*-(*tert*-butoxycarbonyl)-2,3-bis(hydroxymethyl) indole **206** (590 mg, 2.12 mmol, 1 equiv.), manganese dioxide (1.84 g, 21.2 mmol, 10 equiv.) and methyl (triphenylphosphoranylidene)acetate **52** (2.83 g, 8.48 mmol, 4 equiv.) were combined to afford the desired product as yellow solid (150 mg, 0.39 mmol, 18%). **268**: R_f = 0.55 (7:3 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO_4); m.p. 143-145 °C; $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): δ = 1.68 (s, 9H, H_8), 3.85 (s, 6H, H_1 , H_{19}), 6.08 (d, J = 16 Hz, 1H, H_{17}), 6.66 (d, J = 16 Hz, 1H, H_3), 7.36 (d, J = 7.1 Hz, 1H, H_{10}), 7.42 (d, J = 7.8 Hz, 1H, H_{11}), 7.81 (d, J = 16.1 Hz, 1H, H_{11}), 7.89 (d, J = 7.8 Hz, 1H, H_{16}), 8.07 (d, J = 15.2 Hz, 1H, H_{14}), 8.25 (d, J = 16 Hz, 1H, H_4); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3 , 25 °C): δ = 28.2 (C8), 51.8 (C1), 52.0 (C19), 85.7 (C7), 115.9 (C4), 118.2 (C14), 120.2 (C16), 120.6 (C3), 124.1 (C11), 124.8 (C17), 126.3 (C12), 126.9 (C15), 135.4 (C13), 136.3 (C10), 136.7 (C9), 137.0 (C8), 149.6 (C6), 166.3 (C1, 19); IR (KBr): ν_{max} (cm^{-1}) = 3009, 2988, 2953, 2900, 1728,

1629, 1453, 1394, 1370, 1341 , 1332, 1272, 1154, 1035, 970, 895 , 865 , 731;

MS (ESI), 386 (MH^+), HRMS (ESI) m/z : calcd for $C_{21}H_{24}NO_6$ [M^+]: 386.1603, found: 386.1606, -1.84 ppm error.

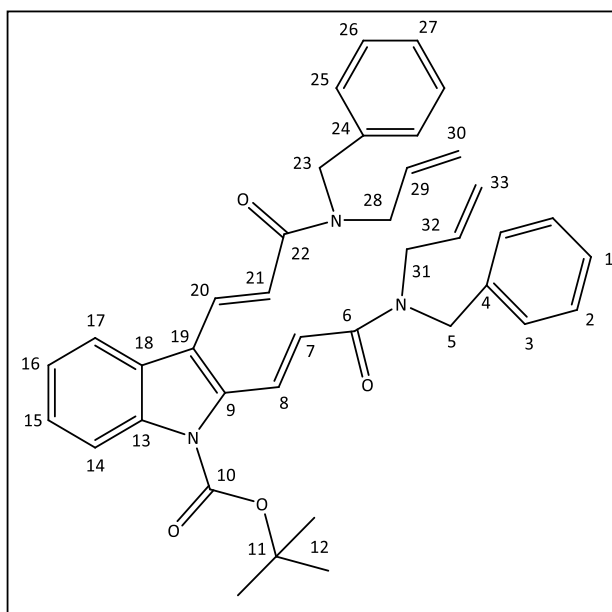
Preparation of *N,N*-diallyl-3,3'-(*N*-(*tert*-butoxycarbonyl)-1*H*-indole-2,3-diyl) diacetamide **269:**



According to **general procedure 5** using *N*-(*tert*-butoxycarbonyl)-2,3-bis(hydroxymethyl) indole **206** (500 mg, 1.8 mmol, 1 equiv.), manganese dioxide (1.56 g, 18 mmol, 10 equiv.) and of *N,N*-diallyl(triphenylphosphoranylidene) acetamide **252** (3.6 g, 9 mmol, 5 equiv.) were combined to afford the desired product as yellow oil (270 mg, 0.92 mmol, 29%). **269**: R_f = 0.56-0.6 (1:1 to 6:4 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: $KMnO_4$); 1H -NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.6 (s, 9H, H_{10}), 4.07-4.12 (m, 8H, H_3 , H_{21}), 5.19-5.31 (m, 8H, H_1 , H_{23}), 5.82-5.88 (m, 4H, H_2 , H_{22}), 6.87 (d, J = 14.9 Hz, 1H, H_5), 6.94 (d, J = 15.4 Hz, 1H, H_{19}), 7.29-7.33 (m, 1H, H_{13}), 7.38-7.40 (m, 1H, H_{14}), 7.74 (d, J = 7.3 Hz, 1H, H_{12}), 7.8 (d, J = 8.3 Hz, 1H, H_{18}),

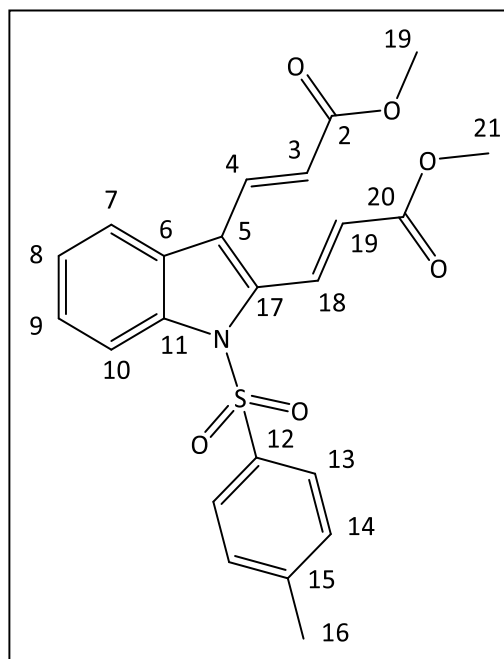
7.88 (d, $J = 14.9$ Hz, 1H, H_6), 8.27 (d, $J = 8.1$ Hz, 1H, H_{15}); ^{13}C -NMR (100 MHz, CDCl_3 , 25 °C): $\delta = 28.2$ (C10), 48.9, 49.0, 49.4, 49.5 (C3, C3', C21, C21'), 83.3 (C9), 115.4 (C5), 115.9 (C15), 116.9, 116.8, 117.7 (C1, C1', C23, C23'), 119.6 (C19), 120.0 (C12), 120.5 (C18), 123.7 (C13), 125.3 (C16), 125.7 (C17), 125.8 (C14), 133.1, 133.4 (C2, C22), 134.3 (C11), 134.8 (C6), 136.2 (C7), 166.7 (C8), 167.5 (C4, 20); MS (ESI), 515 (MH^+), HRMS (ESI) m/z : calcd for $\text{C}_{31}\text{H}_{37}\text{N}_3\text{O}_4$ [$(\text{M}+\text{H})^+$]: 515.2784, found: 516.2878, 0.58 ppm error.

Preparation of *N*-allyl-*N*-benzyl 3,3'-(*N*-(*tert*-butoxycarbonyl)-1*H*-indole-2,3-diyl)diacetamide **270:**



According to **general procedure 5** using *N*-(*tert*-butoxycarbonyl)-2,3-bis(hydroxymethyl) indole **206** (370 mg, 1.33 mmol, 1 equiv.), manganese dioxide (1.15 g, 13.3 mmol, 10 equiv.) and *N*-allyl-*N*-benzyl (triphenylphosphoranylidene) acetamide **253** (2.98 g, 6.65 mmol, 5 equiv.) were combined to afford the crude as yellow oil, which was used without further purification. No characterisation of **270** was attempted.

Preparation of dimethyl 3,3'-(*N*-(toluene-4-sulfonyl)-1*H*-indole-2,3-diyl)diacrylate **271**:

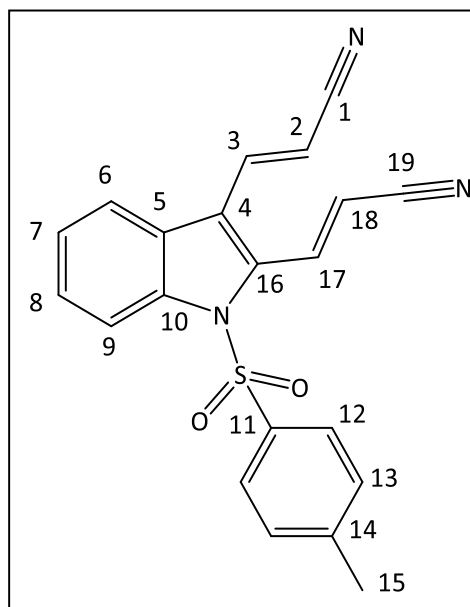


According to **general procedure 5** using *N*-(toluene-4-sulfonyl)-2,3-bis(hydroxymethyl) indole **207** (220 mg, 0.66 mmol, 1 equiv.), manganese dioxide (573 g, 6.6 mmol, 10 equiv.) and methyl (triphenylphosphoranylidene)-acetate **52** (551 mg, 1.65 mmol, 2.5 equiv.) were combined to afford the desired product as yellow oil (150 mg, 0.34 mmol, 51.7%). NMR of the mixture following chromatography showed an inseparable mixture of the intermediate to the desired product in a ~ 4:1 ratio. **271**: R_f = 0.48 (1:1 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO_4); $^1\text{H-NMR}$ (300 MHz, CDCl_3 , selected signals only, 25 °C): δ = 2.33 (s, 3H, H_{16}), 3.82 (s, 6H, $\text{H}_{1,21}$), 3.89 (s, 3H, H_{21}), 6.06 (d, J = 15.8 Hz, 1H, H_3), 6.57 (d, J = 16.2 Hz, 1H, H_{19}), 7.15 (d, J = 8.7 Hz, , 2H, H_{14}), 7.33-7.35 (m, 1H, H_9), 7.60-7.62 (m, 1H, H_{18}), 7.71-7.73 (m, 2H, H_{13}), 7.96 (d, J = 7.3 Hz, 1H, H_{10}), 8.31-8.35 (m, 2H, H_4 , H_8), 8.68 (s, 1H, H_7); $^{13}\text{C-NMR}$ (75

MHz, CDCl₃, 25 °C): δ = 21.6 (C16), 52.2 (C1), 52.8 (C21), 115.3 (C3), 120.9 (C10), 121.3 (C7), 124.9 (C19), 126.6 (C5), 126.8 (C9), 130.0 (C8), 131.2 (C13), 133.4 (C6), 134.5 (C14), 135.9 (C18), 138.5 (C12), 140.1 (C11), 140.5 (C4), 142.0 (C17), 142.1 (C15), 165.9 (C1, 21); IR (neat): ν_{max} (cm⁻¹) = 2972, 2879, 1709, 1626, 1487, 1441, 379, 127, 1195, 1050, 986, 881, 802, 661, 618, 585, 537; Attempts to get high resolution mass spectrometry data failed.

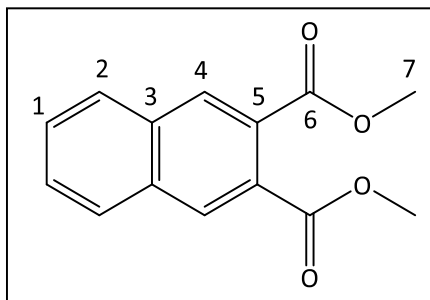
Preparation of 3,3'-(*N*-(toluene-4-sulfonyl)-1*H*-indole-2,3-diyl)diacrylnitrile

272:



According to **general procedure 5** using *N*-(toluene-4-sulfonyl)-2,3-bis(hydroxymethyl) indole **207** (256 mg, 0.77 mmol, 1 equiv.), manganese dioxide (670 g, 67.7 mmol, 10 equiv.) and (triphenylphosphoranylidene)-acetonitrile **265** (580 mg, 1.93 mmol, 2.5 equiv.) were combined to afford the crude **272** as yellow oil, which was used without further purification. No characterisation of **272** was attempted.

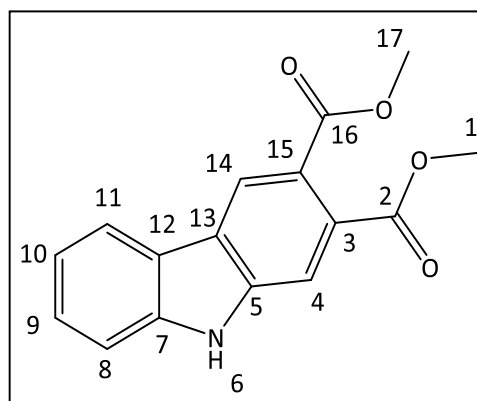
7.2.9 Electrocyclisation of trienes

Preparation of dimethyl-2,3-naphthalenedicarboxylate **274**:**Procedure A:**

The (2*E*,2'*E*)-dimethyl-3,3'-(1,2-phenylen)diacrylate **256** (50 mg) was added to two separate Microwave Biotage Vials with toluene (3 mL). 50 mg of manganese dioxide was added to one of the vials. The vials were sealed and irradiated in a Biotage microwave at 175 °C for 15 min using variable irradiation. Upon completion the vials were cooled to room temperature, unsealed and concentrated *in vacuo* to afford the crude **274**. NMR analysis in both solutions showed no reaction and decomposed of the starting material.

Procedure B:

Two solutions of (2*E*,2'*E*)-dimethyl-3,3'-(1,2-phenylen)diacrylate **256** (50 mg) in 7 mL of diphenyl ether were heated at 250 °C from 15 min to 2 hours. 50 mg of manganese dioxide was added to one of the solutions. The resulted solutions were cooled to room temperature, concentrated *in vacuo* to afford the crude **274**. NMR analysis of the crude **274** in both solutions showed no reaction and decomposed of the starting material.

Preparation of dimethyl carbazole-2,3-dicarboxylate 275:**Procedure A:**

The dimethyl 3,3'-(*N*-(*tert*-butoxycarbonyl)-1H-indole-2,3-diyl)diacrylate **268** (50 mg) was added to a Microwave Biotage Vial with toluene (3 mL). The vial was sealed and irradiated in a Biotage microwave at 175 °C for 15 min using variable irradiation. Upon completion the vial was cooled to room temperature, unsealed and concentrated *in vacuo* to afford the products. NMR analysis showed no reaction and decomposed of the starting material.

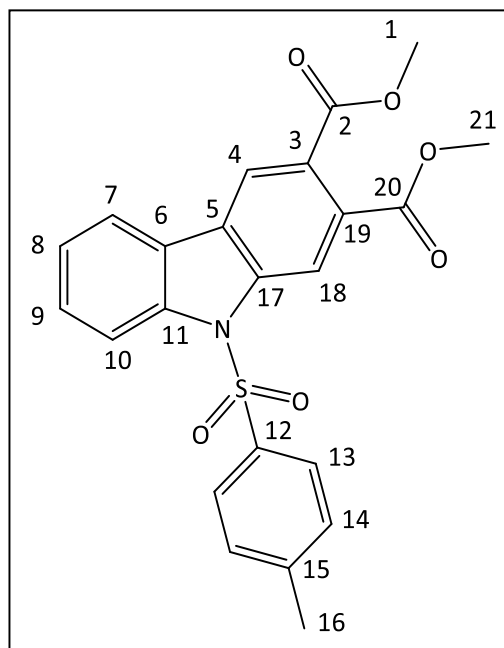
Procedure B:

10% palladium on carbon (190 mg, 0.182 mmol, 1.4 equiv.) was suspended in bromobenzene (12 mL), followed by adding dimethyl 3,3'-(*N*-(*tert*-butoxycarbonyl)-1H-indole-2,3-diyl)diacrylate **268** (50 mg, 0.13 mmol, 1 equiv.). The resulting solution was stirred and heated at reflux for 15 hours and then concentrated *in vacuo*. The residue was heated again with further of 10% Palladium on carbon in bromobenzene for 5 hours, the solvent evaporated, and the residue purified by column chromatography on silica gel using 6:4 petroleum ether (b.p. 40-60 °C)/ethyl acetate as the eluent to afford the title

compound **275** (25 mg, 0.08 mmol, 69%). **275**:⁽¹³⁵⁾ R_f = 0.50 (6:4 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO₄); m.p. 220-225 °C; ¹H-NMR (400 MHz, CDCl₃, 25 °C): δ = 3.93 (s, 3H, H₁₇), 3.95 (s, 3H, H₁), 7.27-7.32 (m, 1H, H₉), 7.47 (d, J = 0.9 Hz, 1H, H₈), 7.8 (dd, J = 2.6, 0.9 Hz, 1H, H₁₁), 7.66 (d, J = 0.6 Hz, 1H, H₁₄), 8.08 (dd, J = 7.7, 0.8 Hz, 1H, H₁₀), 8.52 (s, 1H, H₁₄), 8.63 (br.s, 1H, H₆); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 52.6 (C₁₇), 52.8 (C₁), 111.2 (C₁₁), 111.3 (C₁₄), 120.6 (C₉), 121.0 (C₁₀), 121.8 (C₁₅), 122.5 (C₄), 124.4 (C₁₃), 127.4 (C₈), 129.7 (C₁₂), 130.6 (C₇), 133.6 (C₁₃), 140.6 (C₅), 168.3 (C_{1,17}); IR (KBr): ν_{\max} (cm⁻¹) = 3375, 2939, 2675, 1686, 1601, 1434, 1317, 1263, 1074, 728; MS (ESI), 284 (MH⁺), HRMS (ESI+ m/z%): calcd for C₁₆H₁₄NO₄ [(M+H)⁺]: 284.0923, found 284.0925, -0.69 ppm error.

Preparation of dimethyl *N*-(toluene-4-sulfonyl) carbazole-2,3-dicarboxylate

276:



Procedure A:

The dimethyl 3,3'-(*N*-(toluene-4-sulfoyl)-1H-indole-2,3-diyl)diacrylate **271** (50 mg) was added to a Microwave Biotage vial with toluene (3 mL). The vial was sealed and irradiated in a Biotage microwave at 175 °C for (15, 30 min) using variable irradiation. Upon completion the vial was cooled to room temperature, unsealed and concentrated *in vacuo* to afford the products. NMR analysis showed decomposition of the starting material.

Procedure B:

10% Palladium on carbon (670 mg, 0.34 mmol, 1.88 equiv.) was suspended in anhydrous xylene (5 mL), followed by adding dimethyl 3,3'-(*N*-(toluene-4-sulfoyl)-1H-indole-2,3-diyl)diacrylate **271** (150 mg, 0.63 mmol, 1 equiv.). The resulting solution was stirred and heated at reflux for 24 hours and then filtered through celite, washed with hot xylene (5 mL), and concentrated *in vacuo*. The solid residue was crashed with methanol to get the crude. No characterisation of **276** was attempted (decomposition).

Procedure C:

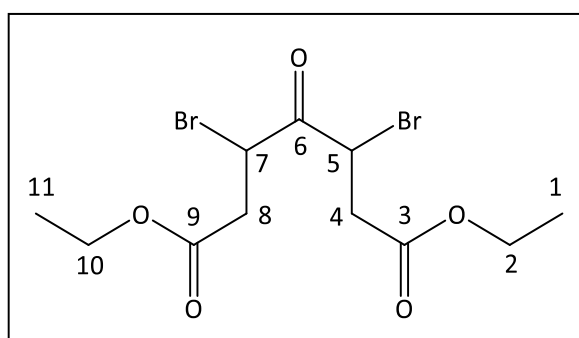
To a solution of dimethyl 3,3'-(*N*-(toluene-4-sulfoyl)-1H-indole-2,3-diyl)diacrylate **271** (150 mg, 0.34 mmol, 1 equiv.) in bromobenzene (7 mL), was added DDQ (154 mg, 0.68 mmol, 2 equiv.) slowly. The resulted solution was heated at reflux for 3 h, filtered through silica gel, evaporated by rotary to give the crude, and then purified using column chromatography on silica gel 95:50 dichloromethane/ methanol as affording the title product **276** as colorless oil

(100 mg, 0.22 mmol, 71%). **276**:⁽¹³⁵⁾ R_f = 0.59 (9.5:0.5 dichloromethane/methanol, det: KMnO_4); $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): δ = 2.28 (d, J = 6.4 Hz, 3H, H_{16}), 3.95 (d, J = 6.4 Hz, 3H, H_1), 4.00 (d, J = 6.4 Hz, 3H, H_{21}), 7.14 (t, J = 7.2 Hz, 2H, H_{14}), 7.38-7.45 (m, 1H, H_{10}), 7.54-7.61 (m, 1H, H_8), 7.68-7.73 (m, 1H, H_{13}), 7.95 (t, J = 6.8 Hz, 1H, H_9), 8.29-8.35 (m, 2H, H_7 , H_{18}), 8.67 (d, J = 6.8 Hz, 1H, H_4); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3 , 25 °C): δ = 21.5 (C_{16}), 52.7 (C_1), 52.9 (C_{21}), 115.1 (C_{18}), 115.5 (C_{10}), 120.7 (C_7), 121.3 (C_4), 124.5 (C_5), 124.9 (C_6), 126.4 (C_8), 126.5 (C_{19}), 127.2 (C_3), 127.9 (2x C_{13}), 128.9 (C_9), 129.9 (2x C_{14}), 131.2 (C_{17}), 134.5 (C_{11}), 139.1 (C_{12}), 139.4 (C_{15}), 167.8 (C_1), 168.1 (C_{21}); IR (KBr): ν_{max} (cm^{-1}) = 3744, 2950, 1732, 1593, 1456, 1377, 1268, 1122, 745; MS (ESI), 438 (MH^+), HRMS (ESI) m/z calcd for $\text{C}_{23}\text{H}_{20}\text{NO}_6\text{S}$ [$(\text{M}+\text{H})^+$] 438.1011, found 438.1009, -0.95 ppm error.

7.3 Experimental procedures: Chapter 3

7.3.1 Wittig reaction of divinyl ketones:

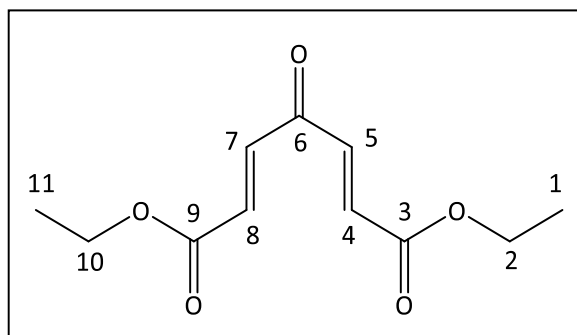
Preparation of diethyl-3,5-dibromo-4-oxoheptadioate **301**:⁽²⁰⁷⁾



To a stirred solution of diethyl 4-oxopimelate **300** (5.0 g, 21.7 mmol, ρ = 1.073 g mL^{-1} , 4.66 mL, 1 equiv.) in anhydrous dichloromethane (10 mL), cooled to 0 °C, a solution of bromine (6.9 g, 43.4 mmol, ρ = 3.119 g mL^{-1} , 2.22 mL, 2 equiv.)

in anhydrous dichloromethane (5 mL) was added dropwise. The mixture was stirred at room temperature for 10 min, and then dichloromethane (50 mL) was added, washed with 1 M sodium thiosulfate (50 mL), dried (MgSO_4) and then concentrated *in vacuo* to afford the title compound **301** as a thick oil (6.7 g, 17.3 mmol, 80%). **301**: $^1\text{H-NMR}$ (400 MHz, CDCl_3 , 25 °C): δ = 1.27 (t, J = 6 Hz, 6H, H_1 , H_{11}), 3.00-3.04 (m, 2H, H_4), 3.25-3.32 (m, 2H, H_8), 4.18 (dd, J = 6.5, 4.8 Hz, H_2 , H_{10}), 5.35 (t, J = 5.6 Hz, 2H, H_5 , H_7); $^{13}\text{C-NMR}$ (100.6 MHz, CDCl_3 , 25 °C): δ = 14.1 (C1, C11), 38.2 (C4, C8), 41.6 (C5, C7), 61.3 (C2, C10), 169.3 (C3, C9), 194.3 (C6); IR (KBr): ν_{max} (cm^{-1}) = 2985, 2940, 1725, 1460, 1375, 1200, 1030, 960, 940, 865, 830, 785, 665; CI-MS (NH_3): 389 (1, $\text{M}+\text{H}^+$), 343 (17, M^+-OEt), 315 (7), 263, 261 (33, $\text{M}^+-\text{OEt}-\text{Br}$), 209, 207 (90), 183, 181 (28), 127 (100), 99 (63).

Preparation of diethyl (*E,E*)-4-oxohepta-2,5-diene-1,7-dioate **302:** ⁽²²²⁾



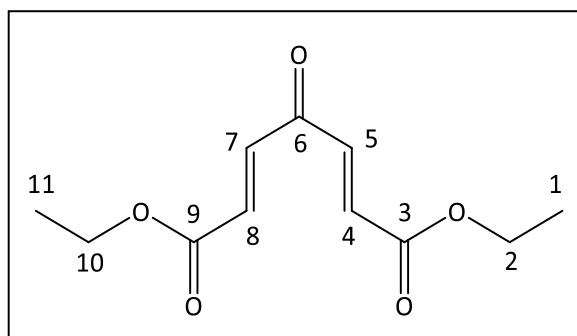
Triethylamine (3.5 g, 34.6 mmol, ρ = 0.725 g mL^{-1} , 4.83 mL, 2 equiv.) was added to a stirred solution of **301** (6.7 g, 17.3 mmol, 1 equiv.) in anhydrous dichloromethane (15 mL) cooled to 0 °C. The resultant mixture was vigorously stirred at 0 °C for 30 min, then water (60 mL) and dichloromethane (50 mL) were added. The organic extract was washed with water (2 \times 100 mL), dried

(MgSO₄), and evaporated the solvent *in vacuo*. Purification *via* flash chromatography on silica using 8:2 petroleum ether (b.p. 40-60 °C)/ethyl acetate obtained **302** as yellow solid (1.5 g, 6.6 mmol, 38%). **302**: R_f = 0.5 (8:2 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO₄); m.p. 49-50 °C; ¹H-NMR (400 MHz, CDCl₃, 25 °C): δ = 1.34 (t, *J* = 7.1 Hz, 6H, H₁, H₁₁), 4.29 (q, *J* = 7.2 Hz, 4H, H₂, H₁₀), 6.81 (d, *J* = 15.9 Hz, 2H, H₄, H₈), 7.23 (d, *J* = 15.9 Hz, 2H, H₅, H₇); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 14.1 (C1, 11), 61.6 (C2, C10), 133.2 (C4, C8), 137.5 (C5, C7), 165.1 (C3, C9), 189.3 (C6); IR (KBr) : ν_{max} (cm⁻¹) = 3070, 2985, 1725, 1675, 1285, 1195, 1090, 1000, 865, 805, 775, 705, 635; CI-MS (NH₃): 226 (34, M⁺), 197 (16, M⁺-Et), 181 (56, M⁺-OEt), 153 (29, M⁺-COOEt), 127 (70), 99 (100); MS (ESI), 227 (MH⁺), HRMS (ESI+ m/z%): calcd for C₁₁H₁₄O₅ [(M+H)⁺]: 226.0841; found 227.0934, -11.78 ppm error.

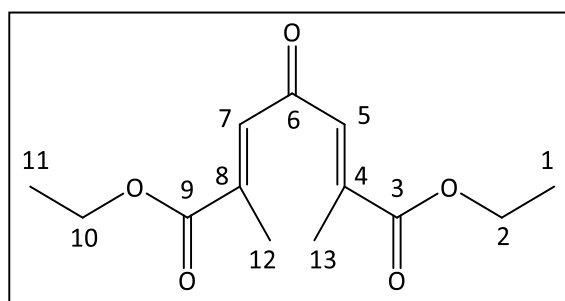
7.3.2 TOP for the preparation of dienes:

General procedure 6:

Activated manganese dioxide (10 equiv.) was added to a stirred solution of diol (1 equiv.) and ylide (2.5 equiv.) in anhydrous THF (20 mL). The resulting solution was stirred and heated at reflux for 24 hours. The manganese dioxide was removed by filtration through a celite pad, washed with THF (50 mL) and the crude was concentrated under higher vacuum, purified by flash chromatography on silica gel using different eluents gave products. Conversion was determined by analysis of the ¹H-NMR spectrum.

Preparation of diethyl (*E,E*)-4-oxohepta-2,5-diene-1,7-dioate **302:**

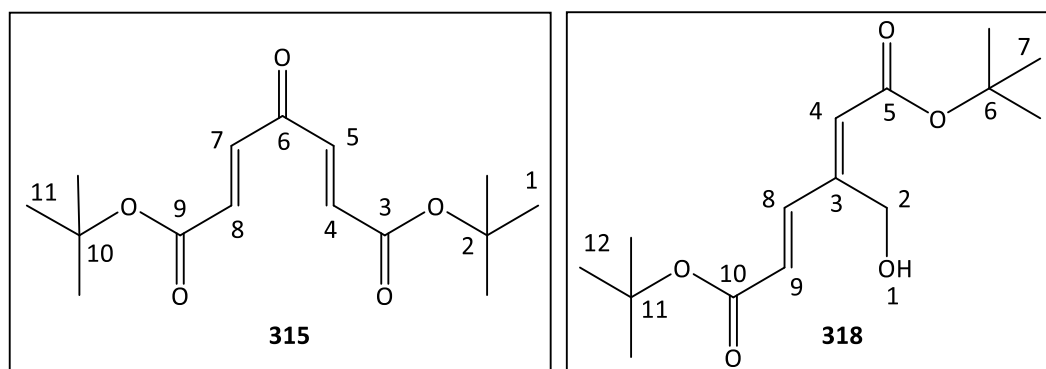
According to **general procedure 6** activated manganese dioxide (2.41 g, 27.8 mmol, 10 equiv.) was added to a stirred solution of dihydroxyacetone **294** (0.5 g, 2.78 mmol, 1 equiv.) and ethyl (triphenylphosphoranylidene)acetate **38** (2.42 g, 6.95 mmol, 2.5 equiv.) in anhydrous THF (20 mL). The resulting solution was concentrated under higher vacuum, purified by flash chromatography on silica gel using 5:5 petroleum ether (b.p. 40-60 °C)/ethyl acetate obtained **302** as yellow solid (90 mg, 0.39 mmol, 15%). Data as recorded in 7.3.1.

Preparation of diethyl (*E,E*)-4-oxohepta-2,5-diene-2,5-dimethyl-1,7-dioate **314:**

According to **general procedure 6** activated manganese dioxide (0.97 g, 11.1 mmol, 10 equiv.) was added to a stirred solution of dihydroxyacetone **294** (200

mg, 1.11 mmol, 1 equiv.) and (carbethoxyethylidene)triphenylphosphorane **35** (1 g, 2.78 mmol, 2.5 equiv.) in anhydrous THF (20 mL). The resulting solution was concentrated under higher vacuum, purified by flash chromatography on silica gel using 1:9 petroleum ether (b.p. 40-60 °C)/ethyl acetate obtained **314** as yellow solid (53 mg, 0.20 mmol, 20%). **314**: R_f = 0.6 (1:9 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO₄); ¹H-NMR (400 MHz, CDCl₃, 25 °C): δ = 1.43 (t, J = 6.4 Hz, 6H, H₁, H₁₁), 2.28 (s, 6H, H₁₂, H₁₃), 4.28 (q, J = 6.3 Hz, 4H, H₂, H₁₀), 7.20 (s, 2H, H₅, H₇); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 14.1 (C₁, C₁₁), 14.5 (C₁₂, C₁₃), 61.7 (C₂, C₁₀), 125.5 (C₅, C₇), 141.9 (C₄, C₈), 165.2 (C₃, C₉), 190.4 (C₆); IR (KBr): ν_{\max} (cm⁻¹) = 2981, 1773, 1627, 1367, 1243, 1173, 1092, 1020, 986, 909, 864; MS (ESI), 255 (MH⁺), HRMS (ESI+ m/z): calcd for C₁₃H₁₉O₅ [(M+H)⁺]: 255.1232, found 255.1230, -1.86 ppm error.

Preparation of (*E,E*)-4-oxohepta-2,5-diene-1,7-di(*tert*-butyl ester) (315**) and β -hydroxy-methyl-(*E,E*)-muconsaeure-di-*tert*-butyl ester (**318**):**



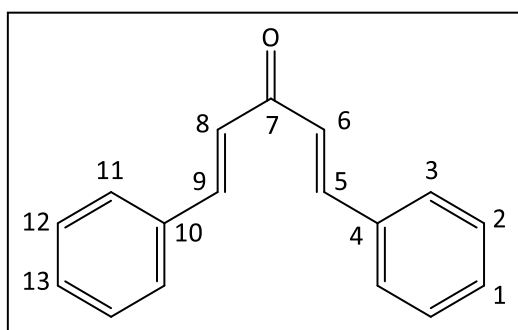
According to **general procedure 6** activated manganese dioxide (0.97 g, 11.1 mmol, 10 equiv.) was added to a stirred solution of dihydroxyacetone **294** (200 mg, 1.11 mmol, 1 equiv.) and (*tert*-butoxycarbonylmethylene)-

triphenylphosphorane **304** (1.04 g, 2.78 mmol, 2.5 equiv.) in anhydrous THF (20 mL). The resulting solution was concentrated under higher vacuum which was used without further purification, afforded yellow oil. TOP reaction of dihydroxyacetone **294** leads to no amounts of **315** compound was isolated.

Instead, the compound **318** was found as a thick oil (70 mg, 0.24 mmol, 22%).

318: $R_f = 0.46$ (8.5:1:0.5 toluene/dichloromethane/acetone, det: KMnO_4); ^1H -NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 1.51$ (d, $J = 3.9$ Hz, 18H, H_7 , H_{12}), 1.83 (br.s, 1H, H_1), 4.42 (br.s, 2H, H_2), 6.03 (d, $J = 16.6$ Hz, 1H, H_8), 6.17 (s, 1H, H_4), 8.32 (d, $J = 16.6$ Hz, 1H, H_9); ^{13}C -NMR (75 MHz, CDCl_3 , 25 °C): $\delta = 28.2$ (C7, C12), 62.6 (C2), 80.9 (C6), 81.3 (C11), 123.4 (C4), 124.6 (C8), 137.0 (C9), 142.2 (C3), 165.0 (C5), 165.7 (C10).

Attempted preparation of 4-oxohepta-2,5-diene-1,7-diphenyl **317:**



According to **general procedure 6** activated manganese dioxide (965 g, 11.1 mmol, 10 equiv.) was added to a stirred solution of dihydroxyacetone **294** (200 mg, 1.11 mmol, 1 equiv.) and benzyltriphenylphosphonium bromide **316** (2.40 g, 5.55 mmol, 5 equiv.) and 7-methyl-1,5,7-triazabicyclo[4.4.0]-dec-5-ene [MTBD] **89** (850 mg, 5.55 mmol, $\rho = 1.067 \text{ g mL}^{-1}$, 790 μL , 5 equiv.) were combined in anhydrous THF (25 mL) were combined. The resulting solution

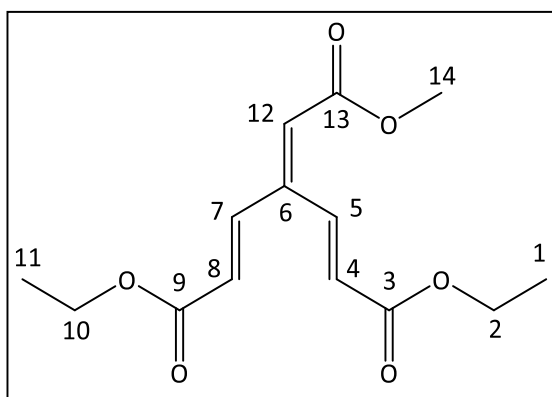
was concentrated under higher vacuum which was used without further purification, afforded yellow oil. No characterisation of **317** was attempted.

7.3.3 Wittig reaction using 4-nitrobenzoic acid (Lewis acid)

General procedure 7:

Diethyl (*E,E*)-4-oxohepta-2,5-dienedioate **302** (1 equiv.), 4-nitrobenzoic acid (0.2 equiv.) and ylides (1.25 equiv.) were combined together in toluene (20-35 mL) and stirred at reflux for 15 hours. The solvent was evaporated *in vacuo* with purification step required by flash chromatography on silica gel using different eluents gave desired products. Conversion was determined by analysis of the ^1H -NMR spectrum.

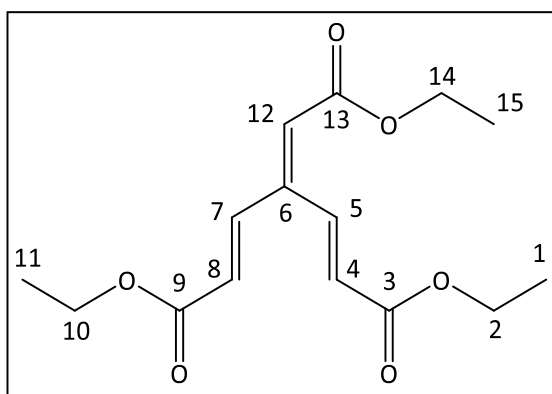
Preparation of diethyl (*E,E*)-4-methylacrylate -2,5-diene-1,7-dioate **303**:



According to **General procedure 7** using diethyl (*E, E*)-4-oxohepta-2,5-dienedioate **302** (100 mg, 0.44 mmol, 1 equiv.), 4-nitrobenzoic acid (13 mg, 0.08 mmol, 0.2 equiv.) and methyl (triphenylphosphoranylidene)acetate **52** (183 mg, 0.55 mmol, 1.25 equiv.) in toluene (20 mL). The title diene was obtained as yellow oil following chromatographic purification from (8:2) petroleum ether (b.p. 40-60 °C)/ethyl acetate (99 mg, 0.35 mmol, 79%). **303**: R_f

= 0.6 (8:2, petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO₄); ¹H-NMR (400 MHz, CDCl₃, 25 °C): δ = 1.33 (t, *J* = 7.1 Hz, 6H, H₁, H₁₁), 3.73 (s, 3H, H₁₄), 4.26 (q, *J* = 7.2 Hz, 4H, H₂, H₁₀), 6.16 (s, 1H, H₁₂), 6.27 (d, *J* = 15.7 Hz, 2H, H₄, H₈), 7.42 (d, *J* = 15.7 Hz, 1H, H₅), 8.28 (d, *J* = 15.9 Hz, 1H, H₇); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 14.2 (C1), 15.3 (C11), 52.0 (C14), 61.6 (C2, C10), 124.0 (C5), 125.9 (C12), 126.4 (C4), 138.2 (C8), 141.6 (C7), 145.9 (C6), 165.4 (C13), 165.7 (C9), 165.8 (C3); IR (neat): ν_{max} (cm⁻¹) = 2983, 2905, 1712, 1165, 1576, 1444, 1367, 1250, 1166, 1035, 980, 747, 712, 559; MS (ESI), 283 (MH⁺), HRMS (ESI+ *m/z*): calcd for C₁₄H₁₉O₆ [(M+H)⁺]: 283.1181, found 283.1176, -2.8 ppm error.

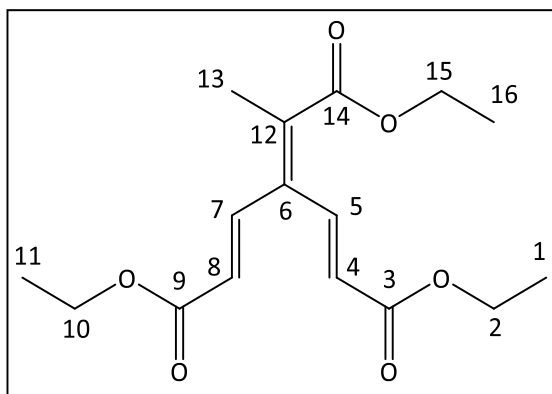
Preparation of diethyl (*E, E*)-4-allylacrylate-2,5-diene-1,7-dioate **308:**



According to **General procedure 7** using diethyl (*E,E*)-4-oxohepta-2,5-dienedioate **302** (500 mg, 2.21 mmol, 1 equiv.), 4-nitrobenzoic acid (73.8 mg, 0.44 mmol, 0.2 equiv.) and ethyl (triphenylphosphoranylidene)acetate **38** (961 mg, 2.76 mmol, 1.25 equiv.) in toluene (30 mL). Purification by flash chromatography on silica using 8:2 petroleum ether (b.p. 40-60 °C)/ethyl acetate afforded the desired compound **308** as yellow oil (286 mg, 0.96 mmol, 43%). **308**: R_f = 0.62 (8:2 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det:

KMnO₄); ¹H-NMR (400 MHz, CDCl₃, 25 °C): δ = 1.33 (t, *J* = 7.1 Hz, 6H, H₁, H₁₁, H₁₅), 4.25-4.29 (m, 6H, H₂, H₁₀, H₁₄), 6.15 (s, 1H, H₁₂), 6.19 (d, *J* = 16.4 Hz, 1H, H₄), 6.27 (d, *J* = 15.7 Hz, 1H, H₈), 7.42 (d, *J* = 15.7 Hz, 1H, H₇), 8.29 (d, *J* = 16.4 Hz, 1H, H₅); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 14.2 (C₁₅), 14.2 (C₁), 14.3 (C₁₁), 60.9 (C₁₄), 61.0 (C₂), 61.0 (C₁₀), 124.6 (C₁₂), 125.7 (C₄), 126.2 (C₈), 138.4 (C₅), 141.7 (C₇), 145.5 (C₆), 165.0 (C₁₃), 165.7 (C₃), 165.8 (C₉); IR (KBr): ν_{max} (cm⁻¹) = 2984, 2936, 2905, 1717, 1638, 1466, 1368, 1268, 1183, 1030, 986, 738, 668, 570; MS (ESI), 297 (MH⁺), HRMS (ESI⁺ *m/z*%): calcd for C₁₅H₂₁O₆ [(M+H)⁺]: 297.1338, found 297.1336, -1.58 ppm error.

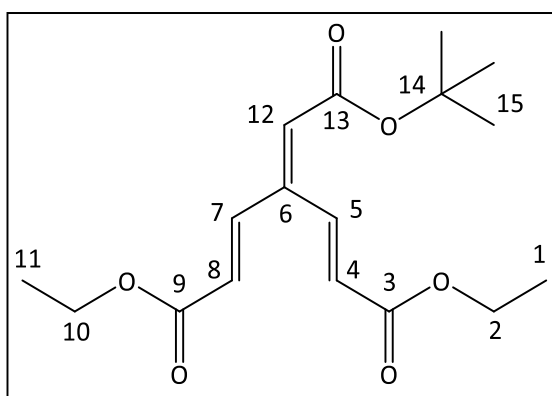
Preparation of diethyl (*E,E*)-4-ethyl methacrylate-2,5-diene-1,7-dioate **309:**



According to **General procedure 7** using diethyl (*E,E*)-4-oxohepta-2,5-dienedioate **302** (500 mg, 2.21 mmol, 1 equiv.), 4-nitrobenzoic acid (73.8 mg, 0.44 mmol, 0.2 equiv.) and (carbethoxyethylidene)triphenylphosphorane **35** (1 g, 2.75 mmol, 1.25 equiv.) in toluene (30 mL) are combined and purified by flash chromatography on silica using 8:2 dichloromethane / diethyl ether to afford the desired compound **309** as yellow oil (650 mg, 2.09 mmol, 95%). **309**: R_f = 0.6 (8:2 dichloromethane/diethyl ether, det: KMnO₄); ¹H-NMR (400 MHz,

CDCl₃, 25 °C): δ = 1.29-1.35 (m, 9H, H₁, H₁₁, H₁₅), 2.12 (s, 3H, H₁₃), 4.20-4.30 (m, 6H, H₂, H₁₀, H₁₅), 5.94 (d, J = 16.1 Hz, 1H, H₄), 6.07 (d, J = 16.1 Hz, 1H, H₈), 7.52 (d, J = 16.1 Hz, 1H, H₇), 7.75 (d, J = 16.1 Hz, 1H, H₅); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 14.1 (C₁₆), 14.3 (C₁), 17.3 (C₁₁), 60.7 (C₁₅), 60.9 (C₂), 61.5 (C₁₀), 123.8 (C₄), 126.3 (C₈), 135.6 (C₁₂), 138.2 (C₆), 139.5 (C₇), 141.1 (C₅), 166.0 (C₁₄), 166.2 (C₃), 168.2 (C₉); IR (neat): ν_{max} (cm⁻¹) = 2974, 1711, 1364, 1159, 1025, 971, 770, 663, 444; MS (ESI), 311 (MH⁺), HRMS (ESI⁺ m/z%): calcd for C₁₆H₂₃O₆ [(M+H)⁺]: 311.1494, found 311.1505, -4.75 ppm error

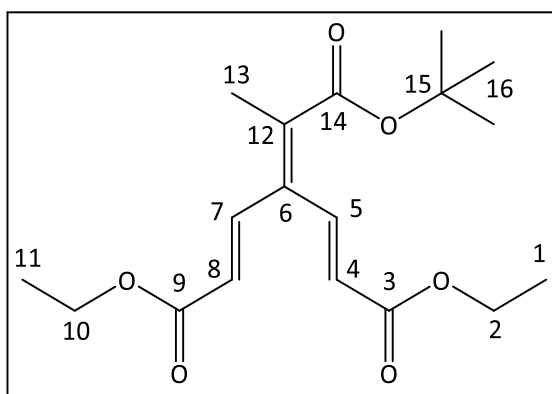
Preparation of diethyl (*E, E*)-4-*tert*-butoxycarbonyl-2,5-diene-1,7-dioate **310:**



According to **General procedure 7** using diethyl (*E, E*)-4-oxohepta-2,5-dienedioate **302** (500 mg, 2.21 mmol, 1 equiv.), 4-nitrobenzoic acid (73.8 mg, 0.44 mmol, 0.2 equiv.) and (*tert*-butoxycarbonylmethylene)triphenylphosphorane **304** (1.3 g, 2.76 mmol, 1.25 equiv.) in toluene (30 mL) were combined and purified by flash chromatography on silica using 8:2 petroleum ether (b.p. 40-60 °C)/ethyl acetate to afford the desired compound **310** as yellow oil (241 mg, 0.74 mmol, 34%). **310**: R_f = 0.5 (8:2 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det:

KMnO_4); $^1\text{H-NMR}$ (400 MHz, CDCl_3 , 25 °C): δ = 1.32 (t, J = 7.2 Hz, 6H, H_1 , H_{11}), 1.51 (s, 9H, H_{15}), 4.25-4.29 (m, 4H, H_2 , H_{10}), 6.14 (d, J = 16.4 Hz, 1H, H_4), 6.24 (d, J = 15.8 Hz, 1H, H_8), 7.39 (d, J = 15.9 Hz, 1H, H_5), 8.24 (d, J = 16.4 Hz, 1H, H_7); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 25 °C): δ = 14.3 (C_1), 15.3 (C_{11}), 28.9 (C_{15}), 60.9 (C_2), 61.0 (C_{10}), 125.3 (C_6), 125.6 (C_4), 126.4 (C_8), 138.7 (C_7), 142.0 (C_5), 144.0 (C_6), 164.3 (C_{13}), 165.8 (C_9), 165.9 (C_3); IR (neat): ν_{max} (cm^{-1}) = 2989, 2942, 1718, 1623, 1393, 1271, 1183, 1114, 1027, 980, 918, 774, 739, 574; MS (ESI), 325 (MH^+), HRMS (ESI $^+$ m/z %): calcd for $\text{C}_{17}\text{H}_{25}\text{O}_6$ [$(\text{M}+\text{H})^+$]: 325.1573, found 325.1561, -5.70 ppm error.

Preparation of diethyl (*E,E*)-4-[*tert*-butyl 2-methyl-2-propionate]-2,5-diene-1,7-dioate 311:



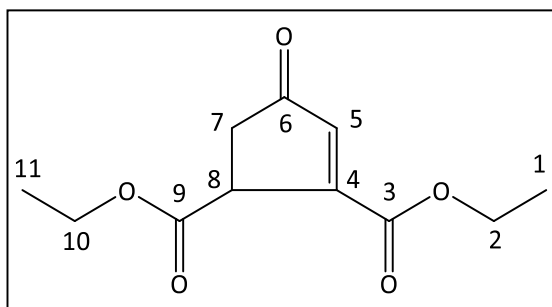
According to **General procedure 7** using diethyl (*E,E*)-4-oxohepta-2,5-dienedioate **302** (230 mg, 1.02 mmol, 1 equiv.), 4-nitrobenzoic acid (34 mg, 0.2 mmol, 0.2 equiv.) and *tert*-butyl 2-(triphenylphosphoranylidene)propionate **305** (500 mg, 1.28 mmol, 1.25 equiv.) were mixed in toluene (10 mL). Purification by flash chromatography on silica using 1:1 petroleum ether (b.p. 40-60 °C)/ethyl acetate afforded the desired compound **311** as yellow oil (160

mg, 0.47 mmol, 47%). **311**: R_f = 0.45 (1:1 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO_4); $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): δ = 1.28-1.35 (m, 6H, $\text{H}_1, \text{H}_{11}$), 1.52 (s, 9H, H_{16}), 2.10 (s, 3H, H_{13}), 4.20-4.29 (m, 4H, $\text{H}_2, \text{H}_{10}$), 5.94 (d, J = 16.1 Hz, 1H, H_4), 6.06 (d, J = 16 Hz, 1H, H_8), 7.51 (d, J = 16 Hz, 1H, H_7), 7.71 (dd, J = 15.9, 0.8 Hz, 1H, H_5); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3 , 25 °C): δ = 14.2 (C_1), 14.2 (C_{11}), 17.2 (C_{13}), 28.0 (C_{16}), 60.6 (C_2), 60.8 (C_{10}), 82.6 (C_{15}), 123.2 (C_4), 125.66 (C_8), 134.0 (C_{12}), 137.7 (C_6), 139.5 (C_7), 141.2 (C_5), 166.0 (C_{14}), 166.2 (C_3), 167.8 (C_9); IR (neat): ν_{max} (cm^{-1}) = 2983, 2938, 2906, 1713, 1622, 1477, 1393, 1255, 1160, 1118, 1031, 979, 932, 773, 672, 564; MS (ESI), 339 (MH^+), HRMS (ESI^+ m/z): calcd for $\text{C}_{18}\text{H}_{27}\text{O}_6$ [$(\text{M}+\text{H})^+$]: 339.1807, found 339.1809, -4.55 ppm error.

7.3.4 Nazarov cyclisation of divinyl ketones

Attempted Preparation of diethyl-4-oxocyclopent-2-ene-1,2-dicarboxylate

319:



Procedure A:

To a solution of diethyl (*E,E*)-4-oxohepta-2,5-diene-1,7-dioate **302** (50 mg, 0.22 mmol, 1 equiv.), in anhydrous dichloromethane (5 mL) was added *p*-toluenesulfonic acid monohydrate (41.8 mg, 0.22 mmol, 1 equiv.) or zirconium

tetrachloride (51.2 mg, 0.22 mmol, 1 equiv.). The resulted solution was stirred at room temperature or 50 °C under a nitrogen pressure. After 15 hours, the reaction mixture was poured into water (20 mL). The aqueous layers were extracted with diethyl ether (3 × 15 mL), washed with saturated brine (50 mL), and then dried (MgSO₄). The filtrate was concentrated *in vacuo*.

Procedure B:

To a solution of diethyl (*E,E*)-4-oxohepta-2,5-diene-1,7-dioate **302** (50 mg, 0.22 mmol, 1 equiv.), in anhydrous dichloromethane (5 mL) was added ferric chloride (35.6 mg, 0.22 mmol, 1 equiv.). The resulted solution was stirred at room temperature or 50 °C under a nitrogen pressure. After 15 hours, the reaction mixture was poured into water (20 mL). The aqueous layers were extracted with ethyl acetate (3 × 15 mL), and then dried (MgSO₄). The filtrate was concentrated *in vacuo*.

Procedure C:

To a cooled solution at 0 °C of diethyl (*E,E*)-4-oxohepta-2,5-diene-1,7-dioate **302** (50 mg, 0.22 mmol, 1 equiv.) in anhydrous dichloromethane (5 mL), titanium tetrachloride [1M in dichloromethane] (260 µL, 0.22 mmol, 1 equiv.) was added. The resulted solution was stirred at room temperature for 15 h, further heating was required. Saturated sodium bicarbonate (5 mL) was added. The aqueous layers were extracted with dichloromethane (3 × 5 mL). The organic layers were combined and dried (MgSO₄). The filtrate was concentrated *in vacuo*.

Procedure D:

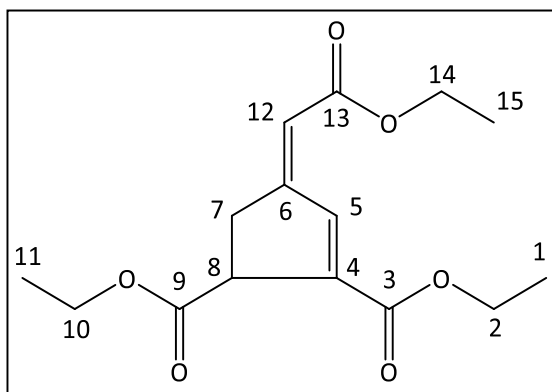
To a solution of diethyl (*E,E*)-4-oxohepta-2,5-diene-1,7-dioate **302** (50 mg, 0.22 mmol, 1 equiv.) in anhydrous dichloromethane (5 mL), bismuth(III) triflate (144 mg, 0.22 mmol, 1 equiv.) was added. The resulted solution was stirred at room temperature for 15 h, further heating was required. The resulted mixture was poured into water (20 mL). The aqueous layers were extracted with diethyl ether (3 × 15 mL), washed with saturated brine (50 mL), and then dried (MgSO₄). The filtrate was concentrated *in vacuo*.

Procedure E:

To a solution of diethyl (*E,E*)-4-oxohepta-2,5-diene-1,7-dioate **302** (50 mg, 0.22 mmol, 1 equiv.) in anhydrous dichloromethane (5 mL), triflic acid (33 mg, 0.22 mmol, $\rho = 1.696 \text{ g mL}^{-1}$, 19 μL , 1 equiv.) was added. The resulted solution was stirred at room temperature for 15 h. The resulted mixture was poured into water (20 mL). The aqueous layers were extracted with ethyl acetate (2 × 20 mL), washed with saturated brine (50 mL), and then dried (MgSO₄). The filtrate was concentrated *in vacuo*. Conversion was determined by analysis of the ¹H-NMR spectrum.

The crudes from (A-E) procedures were obtained as oils with a mass recovery of 90-96, which were used without further purification. No characterisation of **319** was attempted of all these methods.

Preparation of diethyl-4-(ethylmethylenester)cyclopent-2-ene-1,2-dicarboxylate **322**:



Procedure A:

To a solution diethyl (*E,E*)-4-methylacrylate-2,5-diene-1,7-dioate **308** (50 mg, 0.168 mmol, 1 equiv.) in anhydrous dichloromethane (5 mL) acetonitrile (5 mL), *p*-toluenesulfonic acid monohydrate (31.9 mg, 0.168 mmol, 1 equiv.) or zirconium tetrachloride (39.1 mg, 0.168 mmol, 1 equiv.) were added. The resulted solution was stirred at over diethyl ether (3 × 15 mL), washed with saturated brine (50 mL), then dried (MgSO₄). The filtrate was concentrated *in vacuo*.

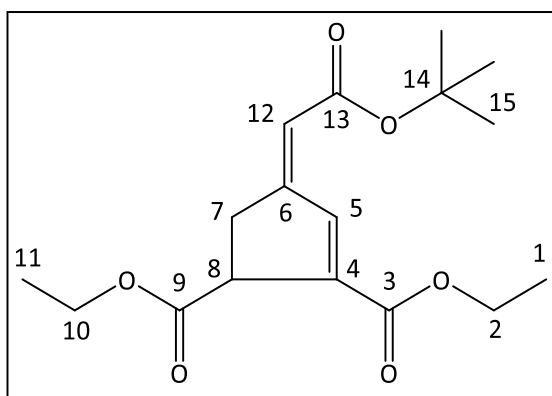
Procedure B:

To a solution of diethyl (*E,E*)-4-methylacrylate-2,5-diene-1,7-dioate **308** (50 mg, 0.168 mmol, 1 equiv.) in anhydrous dichloromethane (5 mL) or acetonitrile (5 mL), ferric chloride (27.2 mg, 0.168 mmol, 1 equiv.) was added. The resulted solution was stirred at room temperature or 50 °C under a nitrogen pressure. After 15 hours, the reaction mixture was poured into water (20 mL). The

aqueous layers were extracted with ethyl acetate (3 × 15 mL), and then dried (MgSO₄). The filtrate was concentrated *in vacuo*.

The crudes from (**A** and **B**) procedures were obtained as oils with a mass recovery of 85-96, which were used without further purification. No characterisation of **322** was attempted of all these methods.

Preparation of diethyl 4-(*tert*-butoxymethylene ester)cyclopent-1-ene-1,2-dicarboxylate **323:**



Procedure A:

To a solution of diethyl (*E,E*)-4-*tert*-butoxycarbonyl-2,5-diene-1,7-dioate **310** (48 mg, 0.14 mmol, 1 equiv.) in anhydrous dichloromethane (5 mL), *p*-toluenesulfonic acid monohydrate (26.6 mg, 0.14 mmol, 1 equiv.) or zirconium tetrachloride (32.6 mg, 0.14 mmol, 1 equiv.) were added. The resulted solution was stirred at room temperature or 50 °C under a nitrogen pressure. After 15 hours, the reaction mixture was poured into water (20 mL). The aqueous layers were extracted with diethyl ether (3 × 15 mL), washed with saturated brine (50 mL), and then dried (MgSO₄). The filtrate was concentrated *in vacuo*.

Procedure B:

To a cooled solution at 0 °C of diethyl (*E,E*)-4-*tert*-butoxycarbonyl-2,5-diene-1,7-dioate **310** (48 mg, 0.14 mmol, 1 equiv.) in anhydrous dichloromethane (5 mL), titanium tetrachloride [1M in dichloromethane] (170 µL, 0.14 mmol, 1 equiv.) was added. The resulted solution was stirred at room temperature for 15 hours, further heating was required. Saturated sodium bicarbonate (5 mL) was added. The aqueous layers were extracted with dichloromethane (3 × 5 mL). The organic layers were combined and dried (MgSO₄). The filtrate was concentrated *in vacuo*.

Procedure c:

To a solution of diethyl (*E,E*)-4-*tert*-butoxycarbonyl-2,5-diene-1,7-dioate **310** (48 mg, 0.14 mmol, 1 equiv.) in anhydrous dichloromethane (5 mL), ferric chloride (23 mg, 0.14 mmol, 1 equiv.) was added. The resulted solution was stirred at room temperature or 50 °C under a nitrogen pressure. After 15 hours, the reaction mixture was poured into water (20 mL). The aqueous layers were extracted with ethyl acetate (3 × 15 mL), and then dried (MgSO₄). The filtrate was concentrated *in vacuo*.

Procedure D:

To a solution of diethyl (*E,E*)-4-*tert*-butoxycarbonyl-2,5-diene-1,7-dioate **310** (48 mg, 0.14 mmol, 1 equiv.) in anhydrous dichloromethane (5 mL), bismuth(III) triflate (92 mg, 0.14 mmol, 1 equiv.) was added. The resulted solution was stirred at room temperature for 15 h, further heating was

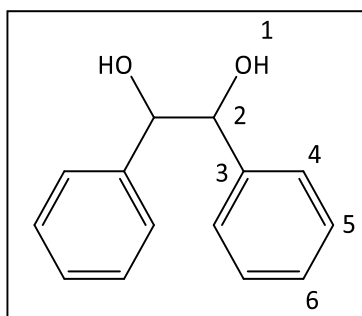
required. The resulted mixture was poured into water (20 mL). The aqueous layers were extracted with diethyl ether (3 × 15 mL), washed with saturated brine (50 mL), and then dried (MgSO₄). The filtrate was concentrated *in vacuo*.

The crudes from (A-D) procedures were obtained as oils with a mass recovery of 80-95, which were used without further purification. No characterisation of **323** was attempted of all these methods.

7.4 Experimental procedures: Chapter 4

7.4.1 Preparation of diols

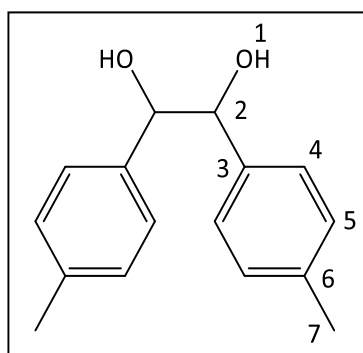
Preparation of 1,2-diphenylethane-1,2-diol **368**:⁽¹⁷⁷⁾



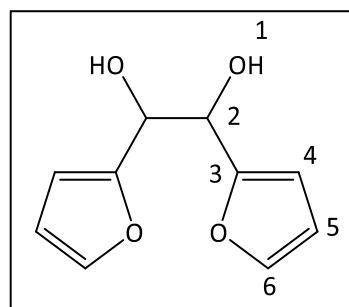
To a solution of benzoin **418** (5.0 g, 35.55 mmol, 1 equiv.) in methanol (160 mL) at 0 °C, sodium borohydride (1.36 g, 35.95 mmol, 1.01 equiv.) was added in several portions. The mixture was stirred for 16 h. The excess of sodium borohydride was poured into cold water (50 mL). Organic layer was extracted with (200 mL) of dichloromethane, dried (MgSO₄), filtered and evaporated by *vacuo* to afford the title diol **368** as white powder (4.5 g, 21 mmol, 90%). **368**: m.p. 137-138 °C; ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 2.19 (s, 2H, H₁), 4.85 (s, 2H, H₂), 7.28-7.30 (m, 4H, H₅), 7.31-7.32 (m, 4H, H₄), 7.33 (dd, *J* = 1.8, 1.0 Hz, 2H, H₆); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 78.1 (C₂), 127.1 (C₅), 128.2 (C₄),

128.3 (C6), 139.8 (C3); IR (KBr) : ν_{\max} (cm⁻¹) = 3372, 3312, 3063, 2899, 1495, 1450, 1279, 1034, 1022, 754, 698, 529; MS (ESI) 237 (MNa⁺), HRMS (ESI, m/z %) Calcd for C₁₄H₁₅O₂ [(M+Na)⁺]: 237.0891; found 237.0894, -3.55 ppm error.

Preparation of 1,2-ditolylethane-1,2-diol **372:** ⁽¹⁷⁷⁾



To a solution of 4,4'-dimethylbenzil **371** (2.0 g, 8 mmol, 1 equiv.) in methanol (80 mL) at 0 °C, sodium tetrahydroborate (770 mg, 20 mmol, 2.5 equiv.) was added in several portions. The mixture was stirred for 16 h. The excess of sodium tetrahydroborate was quenched with cold water (50 mL). Organic layer was extracted with (100 mL) of dichloromethane, dried (MgSO₄), filtered and evaporated *in vacuo* to afford the title diol **372** as white solid (1.10 g, 4.54 mmol, 100%). **372**: m.p. 180 °C; ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 2.05 (s, 2H, H₁), 2.35 (s, 6H, H₇), 4.75 (s, 2H, H₂), 7.13-7.16 (m, 4H, H₄), 7.19-7.22 (m, 4H, H₅); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 21.2 (C7), 78.1 (C2), 127.1 (C4), 129.1 (C5), 137.0 (C6), 137.9 (C3); IR (KBr) : ν_{\max} (cm⁻¹) = 3354, 3307, 2916, 1559, 1514, 1424, 1065, 1034, 819, 556, 519; FAB MS (m/z): Calcd for C₁₆H₁₈O₂ [(M+Na)⁺]: 265.1204; found 265.3504.

Preparation of 1,2-di(2-furyl)-1,2-ethanediol **374:**

To a solution of furoin **373** (2.0 g, 10.4 mmol, 1 equiv.) in methanol (80 mL) at 0 °C, sodium tetrahydroborate (590 mg, 15.6 mmol, 1.5 equiv.) was added in several portions. The mixture was stirred for 24 h. After this time, the excess of sodium tetrahydroborate was quenched with cold water (50 mL). Organic layer was extracted with (100 mL) of dichloromethane, dried (MgSO₄), then evaporated *in vacuo* to afford the title diol **374** as viscous liquid (220 mg, 21%).

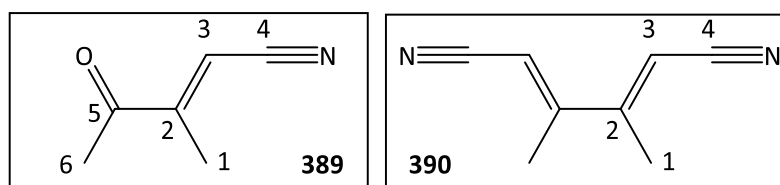
374:⁽¹⁷⁸⁾ ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 3.35 (s, 2H, H₁), 4.97 (s, 2H, H₂), 6.22 (dd, J = 3.4, 0.8 Hz, 2H, H₅), 6.30 (dd, J = 3.3, 1.8 Hz, 2H, H₄), 7.35 (dd, J = 1.9, 0.8 Hz, 2H, H₆); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 70.0 (C2), 108.1 (C5), 110.4 (C4), 142.3 (C6), 152.9 (C3); IR (KBr): ν_{max} (cm⁻¹) = 3392, 2966, 2922, 1607, 1504, 1442, 1147, 1129, 1008, 925, 812; MS (ESI) 217 (MNa⁺), HRMS (ESI, m/z %) Calcd for C₁₀H₈O₂ [(M+Na)⁺]:⁽¹⁶³⁾ 217.0477; found 217.0469.

7.4.2 TOP reactions of diols using different phosphorane ylides**General procedure 8:**

Activated manganese dioxide (10 equiv.) was added to a stirred solution of diol (1 equiv.), phosphorane ylide (2.5 equiv.) with or without 4-nitrobenzoic acid (0.25 equiv.) in toluene (20 mL). The resulting solution was stirred and heated at reflux for 24 h. The manganese dioxide was removed by filtration through a

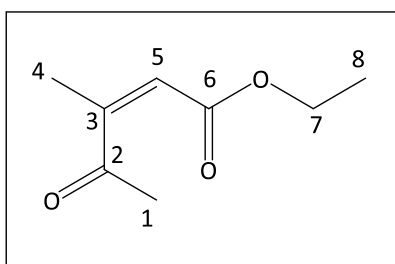
celite pad, washed with THF (50 mL) and the crude was concentrated under higher vacuum, purified by flash chromatography on silica gel using different eluents gave desired products. Conversion was determined by analysis of the ^1H -NMR spectrum.

Attempted preparation of 3-methyl-4-oxopent-2-enenitrile (389) or 3,4-dimethyl-hexadien-2,4-dinitril (390):



According to **general procedure 8** using 2,3-butanediol **350** (100 mg, 1.1 mmol, $\rho = 1.002 \text{ g mL}^{-1}$, 1 mL, 1 equiv.), manganese dioxide (950 mg, 11 mmol, 10 equiv.) and (triphenylphosphoranylidene)acetonitrile **265** (828 mg, 2.75 mmol, 2.5 equiv.) were combined. Concentration *in vacuo* afforded the crude as yellow oil. No characterisation of **389** or **390** was attempted.

Preparation of (*E*)-ethyl 3-methyl-4-oxo-2-pentenoate 376:



Procedure A:

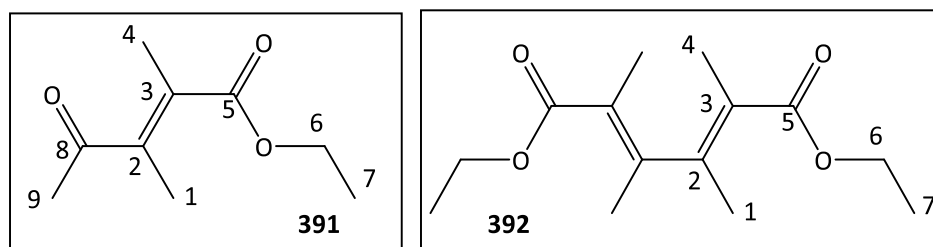
According to **general procedure 8** using 2,3-butanediol **350** (200 mg, 2.21 mmol, $\rho = 1.002 \text{ g mL}^{-1}$, 200 μL , 1 equiv.), manganese dioxide (1.92 g, 22.1 mmol, 10 equiv.) and ethyl (triphenylphosphoranylidene)acetate **38** (1.92 g, 5.52 mmol, 2.5 equiv.) were combined affording the desired product as yellow

oil (100 mg, 0.70 mmol, 32%). **376**: R_f = 0.56 (7:3 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO_4).

Procedure B:

According to **general procedure 8** using 2,3-butanediol **350** (50 mg, 0.55 mmol, ρ = 1.002 g mL^{-1} , 50 μL , 1 equiv.), manganese dioxide (478 mg, 5.5 mmol, 10 equiv.), ethyl 2-(dimethoxyphosphoryl)acetate **381** (269 mg, 1.375 mmol, ρ = 1.186 g mL^{-1} , 220 μL , 2.5 equiv.) and 7-methyl-1,5,7-triazabicyclo[4.4.0]-dec-5-ene [MTBD] **89** (219 mg, 1.43 mmol, ρ = 1.067 g mL^{-1} , 70 μL , 2.6 equiv.) were combined affording the same product as yellow oil (60 mg, 0.38 mmol, 69%). **376**:⁽²²³⁾; $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): δ = 1.31-1.36 (m, 3H, H_8), 2.22 (d, J = 1.3 Hz, 3H, H_4), 2.40 (s, 3H, H_1), 4.24 (q, J = 7.2 Hz, 2H, H_7), 6.59 (q, J = 1.4 Hz, 1H, H_5); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 25 °C): δ = 13.0 (C_4), 14.2 (C_8), 26.8 (C_1), 60.8 (C_7), 126.6 (C_5), 150.4 (C_3), 166.2 (C_6), 200.0 (C_2); IR (neat): ν_{max} (cm^{-1}) = 1725, 1690, 1640; MS (ESI), 156 (MH^+), HRMS (ESI, m/z) calcd. for $\text{C}_8\text{H}_{13}\text{O}_3$ [$(\text{M}+\text{H})^+$]: 156.0864, found 156.0820, -1.5 ppm error.

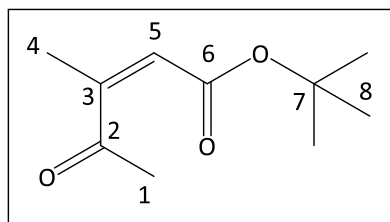
Attempted preparation of ethyl 2,3-dimethyl-4-oxopent-2-enoate (391) or 1,6-dimethyl-3,4-dimethyl-1,6-dicarboethoxy-3,4-butadiene (392):



According to **general procedure 8** using 2,3-butanediol **350** (500 mg, 5.55 mmol, ρ = 1.002 g mL^{-1} , 490 μL , 1 equiv.), manganese dioxide (4.82 g, 55.5 mmol, 10 equiv.) and (carbethoxyethylidene)triphenylphosphorane **35** (5 g,

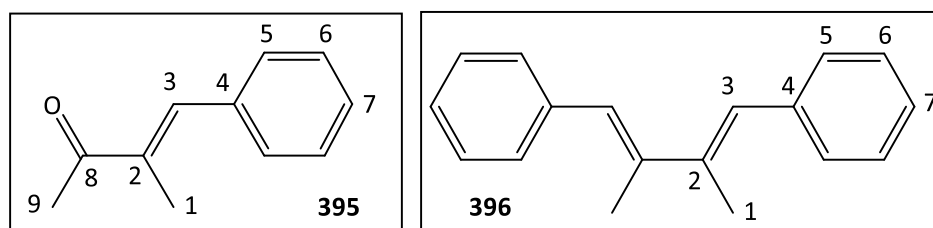
13.87 mmol, 2.5 equiv.) were combined. Concentration *in vacuo* afforded the crude as yellow oil. No characterisation of **391** or **392** was attempted.

Preparation (*E*)-tert-butyl 3-methyl-4-oxopent-2-enoate **393:**



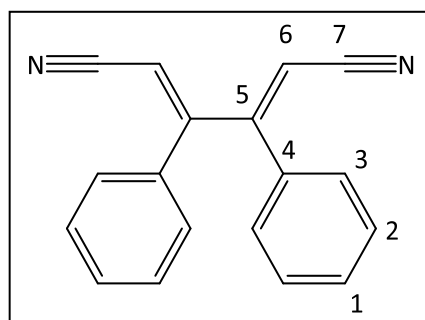
According to **general procedure 8** using 2,3-butanediol **350** (100 mg, 1.10 mmol, $\rho = 1.002 \text{ g mL}^{-1}$, 100 μL , 1 equiv.), manganese dioxide (956 mg, 11.0 mmol, 10 equiv.) and (*tert*-butoxycarbonylmethylene)triphenylphosphorane **304** (1.03 g, 2.75 mmol, 2.5 equiv.) were combined to afford the product as colorless oil (23 mg, 0.124 mmol, 12%). **393**:⁽²²⁴⁾ $R_f = 0.57$ (7:3 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO_4); $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): $\delta = 1.52$ (s, 9H, H_8), 2.17 (d, $J = 1.5 \text{ Hz}$, 3H, H_4), 2.38 (s, 3H, H_1), 6.52 (d, $J = 1.5 \text{ Hz}$, 1H, H_5); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 25 °C): $\delta = 12.8$ (C4), 28.2 (C8), 81.7 (C7), 128.6 (C5), 148.9 (C3), 165.6 (C6), 200.3 (C2); IR (film): $\nu_{\text{max}} (\text{cm}^{-1}) = 2980$, 1716, 1684, 1637, 1366, 1249, 1213, 1152, 1105, 1027, 877, 858, 703; MS (ESI), 207 (MNa^+), HRMS (ESI, $m/z\%$) calcd. for $\text{C}_{10}\text{H}_{16}\text{NaO}_3$ [$(\text{M}+\text{Na})^+$]:⁽²⁰⁹⁾ 207.2240, found 207.0990.

Attempted preparation of 3-methyl-4-phenyl-3-buten-2-one (**395**) or 1,4-diphenyl-2,3-dimethyl-1,3-butadiene (**396**):

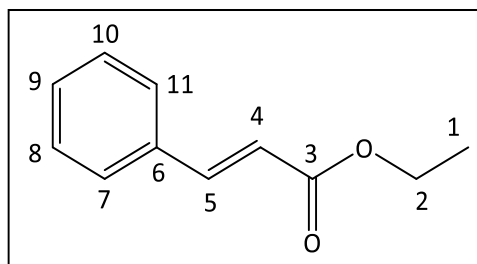


According to **general procedure 8** using 2,3-butanediol **350** (500 mg, 5.55 mmol, $\rho = 1.002 \text{ g mL}^{-1}$, 490 μL , 1 equiv.), manganese dioxide (4.82 g, 55.5 mmol, 10 equiv.), benzyltriphenylphosphonium bromide **316** (5.95 g, 13.75 mmol, 2.5 equiv.) and 7-methyl-1,5,7-triaza-bicyclo[4.4.0]-dec-5-ene [MTBD] **89** (2.19 g, 14.3 mmol, $\rho = 1.067 \text{ g mL}^{-1}$, 2.0 mL, 2.6 equiv.) were combined. Concentration afforded the crude as yellow oil. No characterisation of **395** or **396** was attempted.

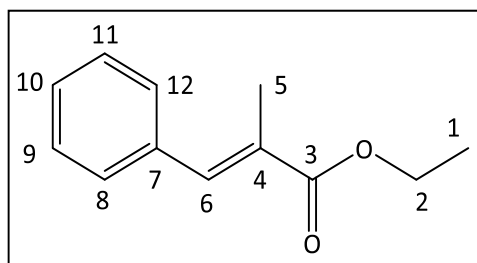
Attempted preparation of 3,4-diphenyl-hexadien-2,4-dinitril **401**:



According to **general procedure 8** using hydrobenzoin **368** (100 mg, 0.47 mmol, 1 equiv.), manganese dioxide (408 mg, 4.7 mmol, 10 equiv.) and (triphenylphosphoranylidene)acetonitrile **265** (354 mg, 1.175 mmol, 2.5 equiv.) were combined, and concentrated *in vacuo* afforded the crude **401** as yellow oil, which used without any purification. No characterisation of **401** was attempted.

Preparation of (*E*)-ethyl cinnamate 397:

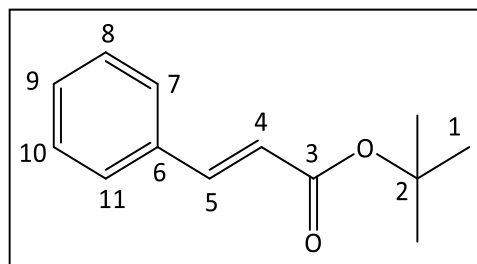
According to **general procedure 8** using hydrobenzoin **368** (200 mg, 0.95 mmol, 1 equiv.), manganese dioxide (825 mg, 9.5 mmol, 10 equiv.) and ethyl (triphenylphosphoranylidene)acetate **38** (827 mg, 2.38 mmol, 2.5 equiv.) were combined affording the product as yellow oil (100 mg, 0.56 mmol, 30.6%). **397**:⁽²²⁵⁾ R_f = 0.63 (7:3 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO_4); $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): δ = 1.34 (t, J = 7.2 Hz, 3H, H_1), 4.27 (q, J = 7.2 Hz, 2H, H_2), 6.44 (d, J = 16 Hz, 1H, H_4), 7.38-7.40 (m, 3H, H_8 , H_9 , H_{10}), 7.53 (dd, J = 6.7, 2.3 Hz, 2H, H_7 , H_{11}), 7.69 (d, J = 16 Hz, 1H, H_5); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 25 °C): δ = 14.4 (C1), 60.5 (C2), 118.3 (C4), 128.1 (C8, C10), 128.9 (C7, C11), 130.3 (C10), 134.5 (C6), 144.6 (C5), 167.1 (C3); IR (neat): ν_{max} (cm^{-1}) = 2998, 2942, 1713, 1638, 1311, 1177; MS (ESI), 177 (MH^+), HRMS (ESI, $m/z\%$): calcd. for $\text{C}_{11}\text{H}_{13}\text{O}_2$ [$(\text{M}+\text{H})^+$]: 177.0915, found 177.0903, 4.5 ppm.

Preparation of (*E*)-ethyl 2-methyl-3-phenylacrylate 403:

According to **general procedure 8** using hydrobenzoin **368** (100 mg, 0.47 mmol, 1 equiv.), manganese dioxide (408 mg, 4.7 mmol, 10 equiv.) and

(carbethoxyethylidene)triphenylphosphorane **35** (425 g, 1.175 mmol, 2.5 equiv.) were combined to give the product as yellow oil (107 mg, 0.28 mmol, 59%). **403**:⁽²²⁶⁾ R_f = 0.70 (7:3 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO_4); $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): δ = 1.32-1.37 (m, 3H, H_1), 2.72 (d, J = 1.5 Hz, 3H, H_4), 4.27 (q, J = 7.2 Hz, 2H, H_2), 7.30-7.33 (m, 1H, H_{10}), 7.38-7.40 (m, 4H, H_9 , H_{11} , H_8 , H_{12}), 7.69 (q, J = 1.3 Hz, 1H, H_6); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 25 °C): δ = 14.1 (C4), 14.4 (C1), 60.9 (C2), 128.3 (C4), 128.1 (C10), 128.4 (C9, C11), 129.7 (C8, C12), 136.0 (C7), 138.7 (C6), 168.7 (C3); IR (neat): ν_{max} (cm^{-1}) = 2980, 1708, 1446, 1253, 1112, MS (ESI), 191 (MH^+), HRMS (ESI, $m/z\%$) calcd. for $\text{C}_{12}\text{H}_{15}\text{O}_2$ [($\text{M}+\text{H}$) $^+$]: 191.1072, found 191.1055, 5.01 ppm error.

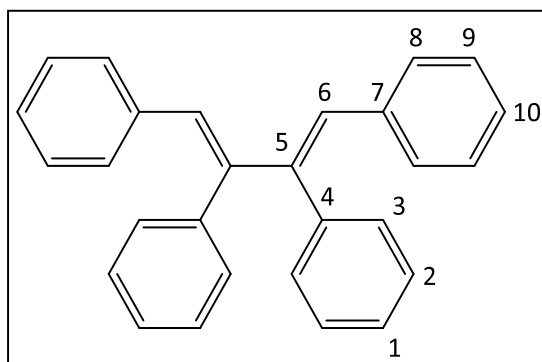
Preparation of (*E*)-*tert*-Butyl cinnamate **404**:



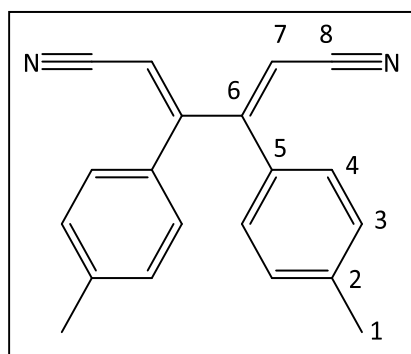
According to **general procedure 8** using hydrobenzoin **368** (100 mg, 0.47 mmol, 1 equiv.), manganese dioxide (408 mg, 4.7 mmol, 10 equiv.) and (*tert*-butoxycarbonylmethylene)triphenylphosphorane **304** (442 g, 1.175 mmol, 2.5 equiv.) were combined to give the product as yellow oil (144 mg, 0.35 mmol, 75%). **404**:⁽²²⁷⁾ R_f = 0.81 (7:3 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO_4); $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): δ = 1.53 (s, 9H, H_1), 6.37 (d, J = 16 Hz, 1H, H_4), 7.34 (d, J = 2.5 Hz, 2H, H_8 , H_{11}), 7.36 (d, J = 1.1 Hz, 1H, H_9), 7.48 (dd, J = 2.3, 0.6 Hz, 1H, H_7), 7.49-7.51 (m, 1H H_{11}), 7.59 (d, J = 16 Hz, 1H, H_5); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 25 °C): δ = 28.2 (C1), 80.5 (C2), 120.2 (C4), 127.0 (C8,

C10), 128.8 (C7, C11), 130.0 (C9), 134.6 (C6), 143.6 (C5), 166.3 (C3); IR (neat): ν_{max} (cm⁻¹) = 3060, 2978, 2931, 1704, 1637, 1577, 1496, 1328, 1315, 1145, 978, 767, 685; MA (ESI), 204 (MH⁺), HRMS (ESI, m/z%) calcd. for C₁₃H₁₆O₂ [(M+H)⁺]⁽²²⁷⁾ 204.1150, found 204.1151.

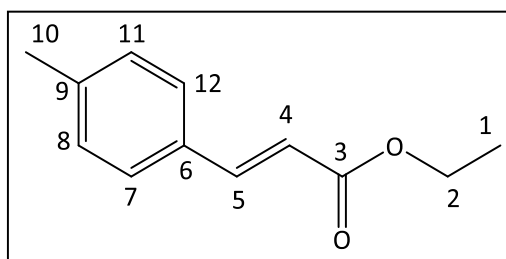
Attempted preparation of 1,2,3,4-tetraphenyl-1,3-butadiene 402:



According to **general procedure 8** using hydrobenzoin **368** (100 mg, 0.47 mmol, 1 equiv.), manganese dioxide (408 mg, 4.7 mmol, 10 equiv.) and benzyltriphenylphosphonium bromide **316** (509 mg, 1.175 mmol, 2.5 equiv.) and 7-methyl-1,5,7-triaza-bicyclo[4.4.0]dec-5-ene [MTBD] **89** (187 mg, 1.22 mmol, ρ = 1.067 g mL⁻¹, 170 μ L, 2.6 equiv.) were combined, concentrated *in vacuo* affording the crude **402** as yellow oil, which used without any purification. No characterisation of **402** was attempted.

Attempted preparation of 3,4-ditolylhexa-2,4-diene-1,6-dinitrile 405:

According to **general procedure 8** using 1,2-di-(4-methylphenyl)-1,2-ethanediol **372** (50 mg, 0.20 mmol, 1 equiv.), manganese dioxide (500 mg, 2 mmol, 10 equiv.) and (triphenylphosphoranylidene)acetonitrile **265** (150 mg, 0.5 mmol, 2.5 equiv.) were combined. Concentration *in vacuo* afforded the crude **405** as yellow oil. No characterisation of **405** was attempted.

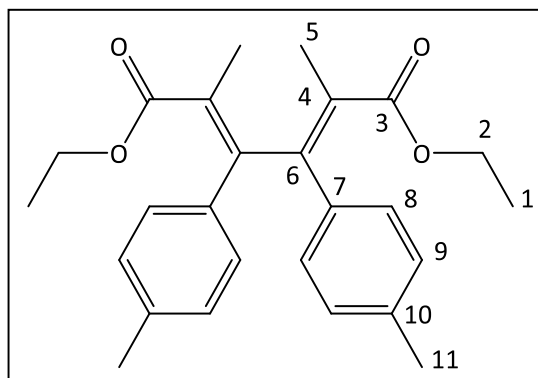
Preparation of ethyl (E)-3-(4-methylphenyl)-2-propenoate 408:**Procedure A:**

According to **general procedure 8** using 1,2-di-(4-methylphenyl)-1,2-ethanediol **372** (50 mg, 0.20 mmol, 1 equiv.), manganese dioxide (500 mg, 2 mmol, 10 equiv.) and ethyl (triphenylphosphoranylidene)acetate **38** (174 mg, 0.5 mmol, 2.5 equiv.) were combined affording the product as yellow oil (39 mg, 0.20 mmol, 100%). **408**: $R_f = 0.57$ (1:1 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO_4).

Procedure B:

According to **general procedure 8** using 1,2-di-(4-methylphenyl)-1,2-ethanediol **372** (50 mg, 0.20 mmol, 1 equiv.), manganese dioxide (500 mg, 2 mmol, 10 equiv.), ethyl 2-(dimethoxyphosphoryl)acetate **381** (98 mg, 0.5 mmol, $p = 1.186 \text{ g mL}^{-1}$, 80 μL , 2.5 equiv.) and 7-methyl-1,5,7-triazabicyclo[4.4.0]-dec-5-ene [MTBD] **89** (79.6 mg, 0.52 mmol, $p = 1.067 \text{ g mL}^{-1}$, 0.07 mL, 2.6 equiv.) were combined affording the same product as yellow oil (17 mg, 0.09 mmol, 43%). **408**:⁽²²⁶⁾ $R_f = 0.6$ (7:3 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO_4); $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): $\delta = 1.31\text{-}1.36$ (m, 3H, H_1), 2.36 (s, H, H_{10}), 4.22-4.30 (m, 2H, H_2), 6.39 (d, $J = 16 \text{ Hz}$, 1H, H_4), 7.19 (d, $J = 8.1 \text{ Hz}$, 2H, H_8 , H_{11}), 7.41-7.43 (m, 2H, H_7 , H_{12}), 7.64-7.69 (m, 1H, H_5); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 25 °C): $\delta = 14.4$ (C1), 21.5 (C10), 60.5 (C2), 117.2 (C4), 128.1 (C5, C12), 128.6 (C8, C11), 131.2 (C9), 140.7 (C6), 144.6 (C5), 167.3 (C3); IR (neat): ν_{max} (cm^{-1}) = 2980 (m), 1708 (s), 1634 (m), 1309 (m), 1163 (s), and 811 (m); MS (ESI), 191 (MH^+), HRMS (ESI, $m/z\%$) calcd. for $\text{C}_{12}\text{H}_{15}\text{O}_2$ [$(\text{M}+\text{H})^+$]:⁽²²⁶⁾ 191.1067, found 191.1063.

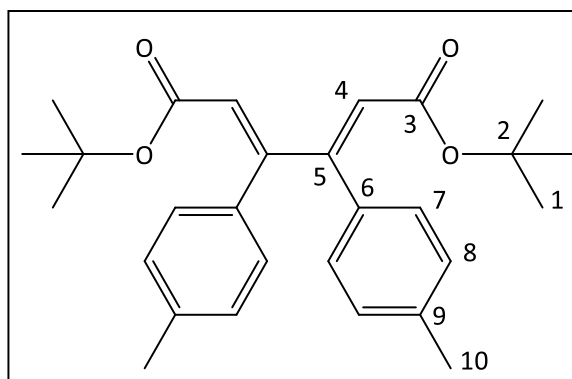
Attempted preparation of 3,4-ditolylhexa-2,4-diene-2,5-dimethyl-1,6-diethyl ester 406:



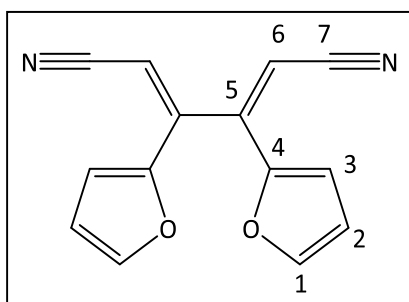
According to **general procedure 8** using 1,2-di-(4-methylphenyl)-1,2-ethanediol **372** (50 mg, 0.20 mmol, 1 equiv.), manganese dioxide (500 mg, 2 mmol, 10 equiv.) and (carbethoxyethylidene)triphenylphosphorane **35** (181 mg, 0.5 mmol, 2.5 equiv.) were combined. Concentration *in vacuo* afforded the crude **406** as yellow oil. No characterisation of **406** was attempted.

Attempted preparation of 3,4-ditolylhexa-2,4-diene-1,6-ditert-butyl ester

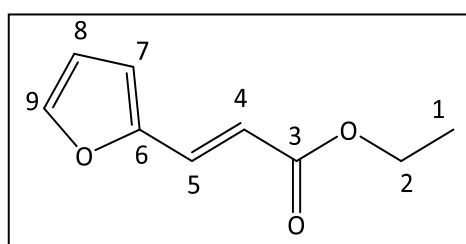
407:



According to **general procedure 8** using 1,2-di-(4-methylphenyl)-1,2-ethanediol **372** (50 mg, 0.20 mmol, 1 equiv.), manganese dioxide (500 mg, 2 mmol, 10 equiv.) and (*tert*-butoxycarbonylmethylene)triphenylphosphorane **304** (188 mg, 0.5 mmol, 2.5 equiv.) were combined. Concentration *in vacuo* afforded the crude **407** as yellow gum. No characterisation of **407** was attempted.

Attempted preparation of 3,4-di-[2]furyl-hexa-2,4-diene-1,6-dinitril **409:**

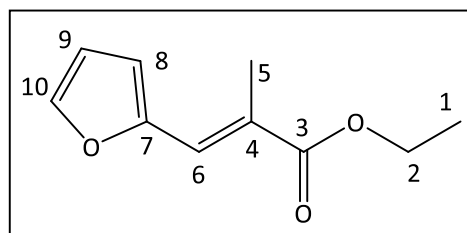
According to **general procedure 8** using 1, 2-di-furan-2-yl-ethane-1, 2-diol **374** (50 mg, 0.25 mmol, 1 equiv.), manganese dioxide (217 mg, 2.5 mmol, 10 equiv.) and (triphenylphosphoranylidene)acetonitrile **265** (188 mg, 0.625 mmol, 2.5 equiv.) were combined. Concentration *in vacuo* afforded the crude **409** as yellow. No characterisation of **409** was attempted.

Preparation of (*E*)-ethyl 3-(furan-2-yl)acrylate **410:**

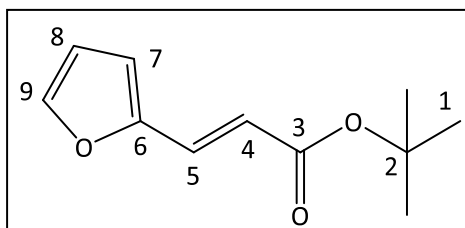
According to **general procedure 8** using 1, 2-di-furan-2-yl-ethane-1,2-diol **374** (50 mg, 0.25 mmol, 1 equiv.), manganese dioxide (217 mg, 2.5 mmol, 10 equiv.), ethyl (triphenylphosphoranylidene)acetate **38** (217 mg, 0.625 mmol, 2.5 equiv.) were combined affording the same product as yellow oil (41 mg, 0.25 mmol, 97%). **410**⁽²²⁶⁾ R_f = 0.6 (1:1 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO₄); ¹H-NMR (300 MHz, CDCl₃, 25 °C): δ = 1.30-1.35 (m, 3H, H₁), 4.21-4.28 (m, 2H, H₂), 6.32 (dd, J = 15.7, 0.5 Hz, 1H, H₈), 6.47 (dd, J = 3.5, 1.8 Hz, 1H, H₄), 6.61 (d, J = 3.2 Hz, 1H, H₅), 7.43 (d, J = 15.6 Hz, 1H, H₇), 7.48 (dd, J = 1.2, 0.7 Hz, 1H, H₉); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 14.3 (C₁),

60.5 (C2), 112.3 (C4), 114.7 (C5), 115.9 (C8), 131.0 (C7), 144.7 (C9), 150.9 (C6), 167.1 (C3); IR (neat): ν_{\max} (cm^{-1}) = 2981, 1708, 1639, 1209, 1164; MS (ESI). 167 (MH^+), HRMS (ESI, $m/z\%$) calcd. for $\text{C}_9\text{H}_{11}\text{O}_3$ $[(\text{M}+\text{H})^+]$: 167.0708, found 167.0711, -4.04 ppm error.

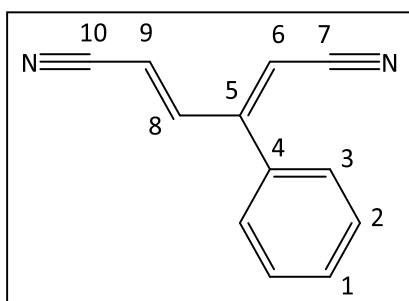
Preparation of ethyl 3-(2-furanyl)-2-methylpropenoate 411:



According to **general procedure 8** using 1, 2-di-furan-2-yl-ethane-1, 2-diol **374** (50 mg, 0.25 mmol, 1 equiv.), manganese dioxide (217 mg, 2.5 mmol, 10 equiv.) and (carbethoxyethylidene)triphenylphosphorane **35** (226 mg, 0.625 mmol, 2.5 equiv.) were combined. Concentration *in vacuo* afforded the crude **411** as yellow oil (25 mg, 0.13 mmol, 54%). **411**:⁽²²⁸⁾ R_f = 0.62 (1:1 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO_4); ^1H -NMR (300 MHz, CDCl_3 , 25 °C): δ = 1.31-1.36 (m, 3H, H_1), 2.22 (s, 3H, H_5), 4.22-4.29 (m, 2H, H_2), 6.49-6.51 (m, 1H, H_8), 6.61 (d, J = 3.4 Hz, 1H, H_{10}), 7.45 (d, J = 0.9 Hz, 1H, H_6), 7.53 (d, J = 1.5 Hz, 1H, H_9); ^{13}C -NMR (100 MHz, CDCl_3 , 25 °C): δ = 14.1 (C5), 14.3 (C1), 60.9 (C2), 112.0 (C8), 114.7 (C10), 125.1 (C4), 125.6 (C6), 144.0 (C9), 152.0 (C7), 168.6 (C3); IR (film): ν_{\max} (cm^{-1}) = 2979, 1705, 1634, 1475, 1372, 1269, 1209, 1176, 1114, 1021, 740; MS (ESI), 181 (MH^+), HRMS (ESI, $m/z\%$) calcd. for $\text{C}_{10}\text{H}_{13}\text{O}_3$ $[(\text{M}+\text{H})^+]$: 181.0864, found 181.0865, -3.09 ppm error.

Preparation of (*E*)-*tert*-butyl 3-(furan-2-yl)acrylate **412:**

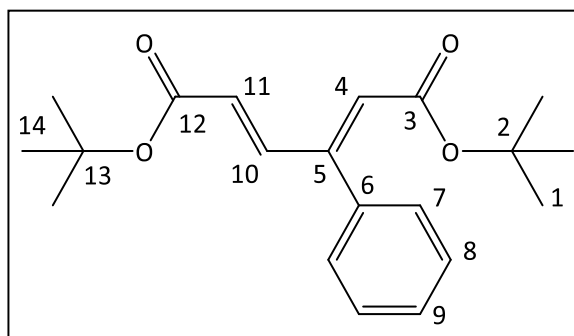
According to **general procedure 8** using 1, 2-di-furan-2-yl-ethane-1,2-diol **374** (50 mg, 0.25 mmol, 1 equiv.), manganese dioxide (217 mg, 2.5 mmol, 10 equiv.) and (*tert*-butoxycarbonylmethylene)triphenylphosphorane **304** (235 mg, 0.625 mmol, 2.5 equiv.) were combined. Concentration *in vacuo* afforded the crude **412** as yellow oil (39 mg, 0.2 mmol, 78%). **412**:⁽²²⁷⁾ R_f = 0.65 (1:1 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO₄); ¹H-NMR (300 MHz, CDCl₃, 25 °C): δ = 1.52 (s, 9H, H₁), 6.22-6.28 (m, 1H, H₈), 6.45 (dd, J = 3.4, 1.9 Hz, 1H, H₄), 6.57 (d, J = 3.4 Hz, 1H, H₆), 7.33 (d, J = 15.6 Hz, 1H, H₇), 7.45-7.47 (m, 1H, H₉); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 28.2 (C1), 80.4 (C2), 112.2 (C4), 114.1 (C5), 118.0 (C8), 130.1 (C7), 144.4 (C9), 151.1 (C6), 166.4 (C3); IR (neat): ν_{\max} (cm⁻¹) = 1705, 1639, 1153; MS (ESI), 217 (MNa⁺), HRMS (ESI, m/z%) calcd. for C₁₁H₁₄NaO₃ [(M+Na)⁺]: 217.0841, found 217.0875.

Attempted preparation of 2-phenyl-1,4-dicyanobuta-1,3-diene **413:**

According to **general procedure 8** using 1-phenyl-1,2-ethanediol **369** (100 mg, 0.72 mmol, 1 equiv.), manganese dioxide (625 mg, 7.2 mmol, 10 equiv.) and

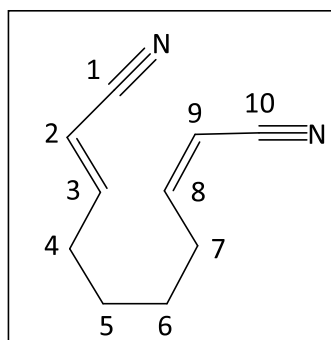
(triphenylphosphoranylidene)acetonitrile **265** (542 mg, 1.8 mmol, 2.5 equiv.) were combined. Concentration *in vacuo* afforded the crude **413** as yellow. No characterisation of **413** was attempted.

Attempted preparation of di-*tert*-butyl -3-phenyl-2,4-hexadienedioate 414:



According to **general procedure 8** using 1-phenyl-1,2-ethanediol **369** (100 mg, 0.72 mmol, 1 equiv.), manganese dioxide (625 mg, 7.2 mmol, 10 equiv.) and (*tert*-butoxycarbonylmethylene)triphenylphosphorane **304** (677 mg, 1.8 mmol, 2.5 equiv.) were combined. Concentration *in vacuo* afforded the crude **413** as yellow oil which was used without further purification. No characterisation of **413** was attempted.

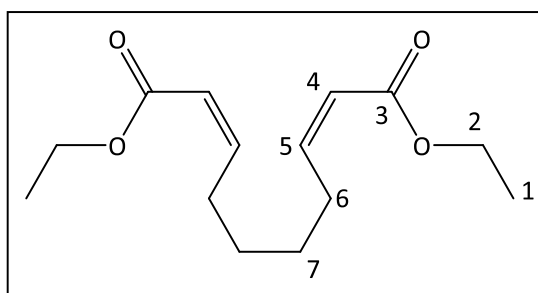
Preparation of (*E,Z*)-deca-2,8-dienedinitrile 419:



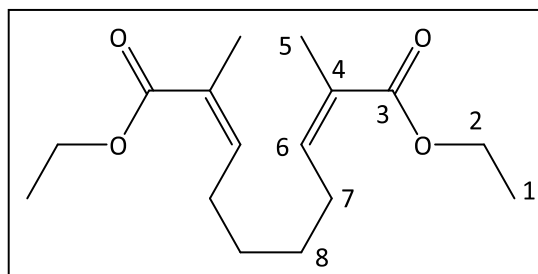
According to **general procedure 8** using 1,2-cyclohexanediol **370** (50 mg, 0.43 mmol, 1 equiv.), manganese dioxide (373 mg, 4.3 mmol, 10 equiv.) and (triphenylphosphoranylidene)acetonitrile **265** (323 mg, 1.075 mmol, 2.5 equiv.)

were combined, and concentrated *in vacuo* affording the title compound **419** as yellow oil (250 mg, 1.5 mmol, 36.7%). **419**: R_f = 0.64 (4:6 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO_4); $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): δ = 1.49 (s, 4H, H_4 , H_7), 2.25 (d, J = 5.1 Hz, 4H, H_5 , H_6), 5.35 (d, J = 16.4 Hz, 2H, H_2 , H_{10}), 6.7 (dt, J = 16.3, 6.9 Hz, 2H, H_3 , H_9); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 25 °C): δ = 27.0 (C4, C7), 33.0 (C5, C6), 100.4 (C2, C9), 117.3 (C1, C10), 155.0 (C3, C8); IR (neat): ν_{max} (cm^{-1}) = 3058, 2934, 2925, 2861, 2220, 1630, 1229, 1073, 973, 916, 868, 778, 746; MS (ESI), 161 (MH^+), HRMS (ESI, $m/z\%$) calcd. for $\text{C}_{10}\text{H}_{13}\text{N}_2$ [$(\text{M}+\text{H})^+$]: 161.1078, found 161.1072, 0.9 ppm error.

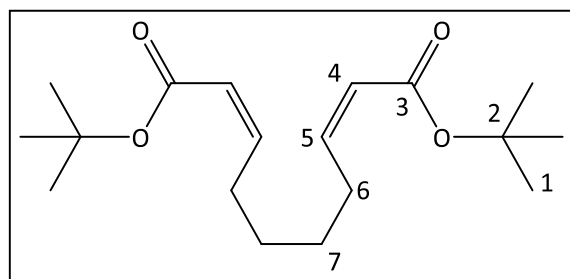
Attempted preparation of deca-2,8-dicarbonsaeurediethylester **415:**



According to **general procedure 8** using 1,2-cyclohexanediol **370** (50 mg, 0.43 mmol, 1 equiv.), manganese dioxide (373 mg, 4.3 mmol, 10 equiv.) and ethyl (triphenylphosphoranylidene)acetate **38** (374 mg, 1.075 mmol, 2.5 equiv.) were combined. The product proved to be inexistent using silica gel and NMR analysis. Thus, the mixture was dissolved in toluene (15 mL), 4-nitrobenzoic acid (17 mg, 0.107 mmol, 0.25 equiv.) added and the mixture was stirred and heated at reflux for 15 hours, concentrated *in vacuo* affording the crude **415** as a yellow oil. No characterisation of **415** was attempted.

Attempted preparation of deca-2,9-dimethyl-2,8-dicarbonsaeure-diethylester**416:**

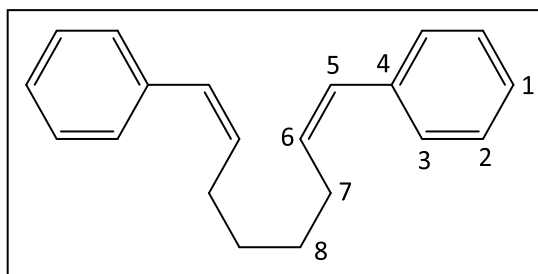
According to **general procedure 8** using 1, 2-cyclohexanediol **370** (50 mg, 0.43 mmol, 1 equiv.), manganese dioxide (373 mg, 4.3 mmol, 10 equiv.) and (carbethoxyethylidene)triphenylphosphorane **35** (389 mg, 1.075 mmol, 2.5 equiv.) were combined. The product proved to be inexistent using silica gel and NMR analysis. Thus, the mixture was dissolved in toluene (10 mL), 4-nitrobenzoic acid (17 mg, 0.107 mmol, 0.25 equiv.) added and the mixture was stirred and heated at reflux for 15 hours, concentrated *in vacuo* affording the crude **416** as a yellow oil, which was used without further purification. No characterisation of **416** was attempted.

Attempted preparation of di-*tert*-butyl deca-2,8-dienedioate 417:

According to **general procedure 8** using 1,2-cyclohexanediol **370** (50 mg, 0.43 mmol, 1 equiv.), manganese dioxide (373 mg, 4.3 mmol, 10 equiv.) and (*tert*-butoxycarbonylmethylene)triphenylphosphorane **304** (404 mg, 1.075 mmol, 2.5 equiv.) were combined, concentrated *in vacuo* affording the crude **417** as a

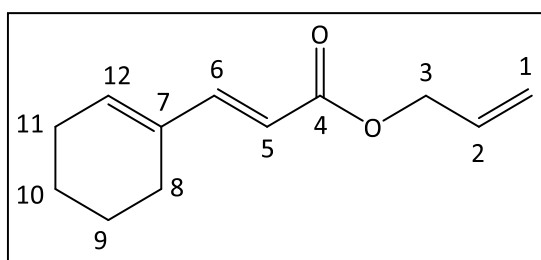
yellow oil, which was used without further purification. No characterisation of **417** was attempted.

Attempted preparation of 1,8-diphenyl-octa-1,7-diene **418:**



According to **general procedure 8** using 1,2-cyclohexanediol **374** (50 mg, 0.43 mmol, 1 equiv.), manganese dioxide (373 mg, 4.3 mmol, 10 equiv.) benzyltriphenylphosphonium bromide **316** (465 mg, 1.075 mmol, 2.5 equiv.) and 7-methyl-1,5,7-triaza-bicyclo[4.4.0]dec-5-ene [MTBD] **89** (171 mg, 1.11 mmol, $\rho = 1.067 \text{ g mL}^{-1}$, 160 μL , 2.6 equiv.) were combined, concentrated *in vacuo* affording the crude **418** as a yellow oil, which was used without further purification. No characterisation of **418** was attempted.

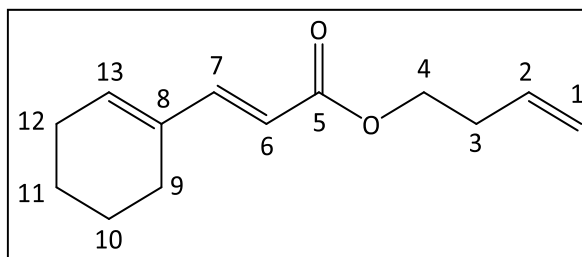
Preparation of allyl 3-(1-cyclohexenyl)acrylate **362:**



According to **general procedure 8** using (1-cyclohexenyl)methanol **357** (455 mg, 4 mmol, 1 equiv.), manganese dioxide (1.7 g, 20 mmol, 5 equiv.), and allyl (triphenylphosphoranylidene) acetate **248** (1.8 g, 5 mmol, 1.25 equiv.) were combined, concentrated *in vacuo* affording the crude **362** as a yellow oil (100

mg, 0.52 mmol, 13%). **362**: R_f = 0.38 (7:3 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO_4); $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): δ = 1.62 (m, 2H, H_{10}), 1.69 (m, 2H, H_9), 2.14 (m, 2H, H_{11}), 2.21 (d, J = 2.7 Hz, 2H, H_{12}), 4.66 (d, J = 5.5 Hz, 2H, H_3), 5.24 (d, J = 10.5 Hz, 1H, H_{1a}), 5.34 (d, J = 17.4 Hz, 1H, H_{1b}), 5.77-5.81 (m, 1H, H_5), 5.96 (d, J = 16.8 Hz, 1H, H_2), 6.18 (s, 1H, H_{12}), 7.31 (d, J = 15.7 Hz, 1H, H_6); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 25 °C): δ = 22.0 (d, J = 3.7 Hz, C9, C10), 24.1, 26.5 (C8, C11), 64.8 (C3), 114.2 (C5), 117.9 (C1), 132.6 (C12), 135.0 (C7), 139.0 (C2), 148.5 (C6), 167.2 (C4); IR (neat): ν_{max} (cm^{-1}) = 3031, 2944, 1702, 1666, 1606, 1581, 1475, 1425, 128, 1185, 1090, 971, 885, 817. 679; MS (ESI), 193 (MH^+), HRMS (ESI, $m/z\%$) calcd. for $\text{C}_{12}\text{H}_{17}\text{O}_2$ [$(\text{M}+\text{H})^+$]: 193.1228, found 193.1242, 2.9 ppm.

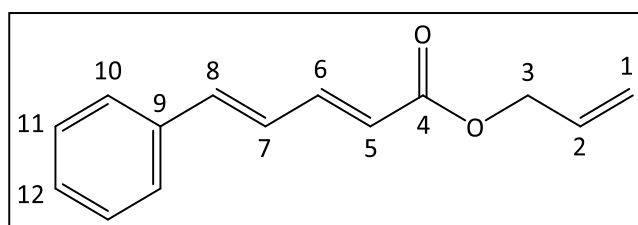
Preparation of 3'-butyen-1'-yl-3-(1-cyclohexenyl)acrylate **363:**



According to **general procedure 8** using (1-cyclohexenyl)methanol **357** (500 mg, 4.5 mmol, 1 equiv.), manganese dioxide (1.95 g, 22.5 mmol, 5 equiv.), and 3'-butyen-1'-yl 2-(triphenylphosphoranylidene)acetate **254** (2.11 g, 5.62 mmol, 1.25 equiv.) were combined, concentrated *in vacuo* affording the crude **363** as a yellow oil (100 mg, 0.04 mmol, 11%). **363**: R_f = 0.50 (7:3 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO_4); $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): δ = 1.64 (d, J = 19.8 Hz, 4H, H_{10} , H_{11}), 2.16 (d, J = 17.7 Hz, 4H, H_9 , H_{12}), 2.43 (d, J =

6.8 Hz, 2H, H₃), 4.16-4.23 (m, 2H, H₄), 5.06-5.15 (m, 1H, 2H, H₁), 5.72-5.90 (m, 2H, H₂, H₇), 6.16 (s, 1H, H₁₃), 7.28 (d, $J = 15.8$ Hz, 1H, H₆); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): $\delta = 22.0, 22.0, 24.1, 26.4$ (C₉, C₁₀, C₁₁, C₁₂), 33.1 (C₃), 63.2 (C₄), 114.3 (C₁), 117.1 (C₆), 134.1 (C₁₃), 134.9 (C₂), 138.8 (C₈), 148.2 (C₇), 167.0 (C₅); IR (neat): ν_{\max} (cm⁻¹) = 2931, 2860, 1702, 1627, 1449, 1618, 1434, 1288, 1162, 1064, 981, 871, 831, 798, 686; MS (ESI), 207 (MH⁺), HRMS (ESI, m/z%) calcd. for C₁₃H₁₉O₂ [(M+H)⁺]: 207.1385, found 207.1391, -5.12 ppm error.

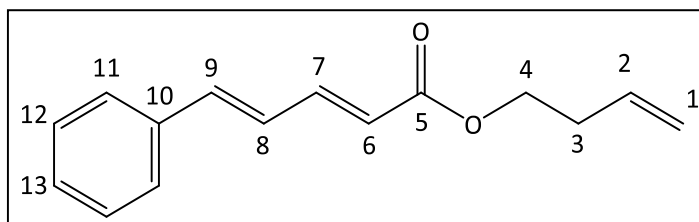
Preparation of 5-phenyl-penta-2,4-dienoic acid allyl ester 353:



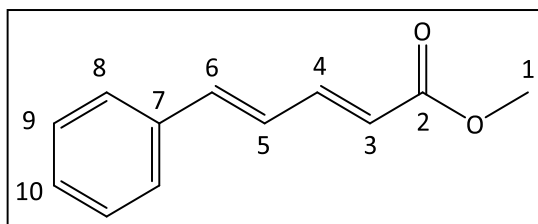
According to **general procedure 8** using cinnamyl alcohol **346** (1 g, 7.45 mmol, $\rho = 1.044$ g mL⁻¹, 950 μ L, 1 equiv.), manganese dioxide (3.2 g, 3.72 mmol, 5 equiv.), and allyl (triphenylphosphoranylidene) acetate **248** (3.35 g, 9.31 mmol, 1.25 equiv.) were combined, concentrated *in vacuo* affording the crude **353** as a yellow oil (510 mg, 2.4 mmol, 32%). **353**: $R_f = 0.55$ (8:2 hexane/ethyl acetate, det: KMnO₄); ¹H-NMR (300 MHz, CDCl₃, 25 °C): $\delta = 4.64$ -4.67 (m, 2H, H₃), 5.24 (dq, $J = 10.5, 1.3$ Hz, 1H, H₁), 5.34 (dq, $J = 17.2, 1.6$ Hz, 1H, H₁), 5.89-5.97 (m, 1H, H₂), 5.99-6.02 (m, 1H, H₅), 6.83 (d, $J = 2.8$ Hz, 1H, H₇), 6.84 (1H, H₈), 7.26-7.35 (m, 3H, H₁₁, H₁₂), 7.40-7.44 (m, 2H, H₁₀), 7.48 (dd, $J = 6.8, 3.6$ Hz, 1H, H₆); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): $\delta = 65.1$ (C₃), 118.1 (C₁), 120.9 (C₂, C₅), 126.2 (C₇), 127.3 (C₁₀), 128.9 (C₁₁), 129.2 (C₁₂), 132.5 (C₉), 140.7 (C₈), 145.1 (C₆), 166.6 (C₄); IR (neat): ν_{\max} (cm⁻¹) = 3027, 2946, 1703, 1647, 1624, 1495,

1449, 1362, 1170, 988, 932, 837, 750, 689; MS (ESI), 215 (MH⁺), HRMS (ESI, m/z%) calcd. for C₁₄H₁₅O₂ [(M+H)⁺]: 215.1072, found 215.1066, 1.26 ppm error.

Preparation of 5-phenyl-hexa-2,4-dienoic acid allyl ester **364:**



According to **general procedure 8** using cinnamyl alcohol **346** (1 g, 7.45 mmol, $\rho = 1.044 \text{ g mL}^{-1}$, 950 μL , 1 equiv.), manganese dioxide (3.2 g, 3.72 mmol, 5 equiv.), and 3'-butyen-1'-yl2-(triphenylphosphoranylidene)acetate **254** (3.5 g, 9.31 mmol, 1.25 equiv.) were combined, concentrated *in vacuo* affording the crude **364** as a yellow oil (534 mg, 2.3 mmol, 31%). **364**: $R_f = 0.57$ (8:2 hexane/ethyl acetate, det: KMnO₄); ¹H-NMR (300 MHz, CDCl₃, 25 °C): $\delta = 2.39\text{--}2.48$ (m, 2H, H₃), 4.21 (t, $J = 6.8 \text{ Hz}$, 2H, H₄), 5.06–5.18 (m, 2H, H₁), 5.73–5.89 (m, 1H, H₂), 5.95–6.00 (m, 1H, H₆), 6.85 (d, $J = 4.1 \text{ Hz}$, 1H, H₈), 6.86 (1H, H₉), 7.28–7.36 (m, 3H, H₁₁, H₁₂), 7.41–7.45 (m, 2H, H₁₀), 7.47–7.52 (m, 1H, H₇); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): $\delta = 33.2$ (C₃), 63.5 (C₄), 117.3 (C₁), 121.2 (C₆), 126.2 (C₁₁), 127.3 (C₈), 128.9 (C₁₃), 129.1 (C₁₂), 134.2 (C₂), 136.0 (C₉), 140.5 (C₁₀), 144.8 (C₇), 167.0 (C₅); IR (neat): $\nu_{\text{max}} (\text{cm}^{-1}) = 2988, 2956, 2901, 1727, 1641, 1495, 1393, 1249, 117, 1066, 970, 866, 791, 698$; MS (ESI), 229 (MH⁺), HRMS (ESI, m/z%) calcd. for C₁₅H₁₇O₂ [(M+H)⁺]: 229.1228, found 229.1224, –0.97 ppm error.

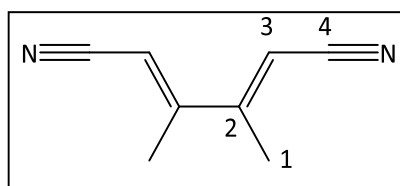
Preparation of methyl 5-phenyl-2,4-pentadienoate 365:

According to **general procedure 8** using cinnamyl alcohol **346** (49.6 mg, 0.37 mmol, $p = 1.044 \text{ g mL}^{-1}$, 47 μL , 1 equiv.), manganese dioxide (160 mg, 1.9 mmol, 5 equiv.), bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate **361** (150 mg, 0.46 mmol, $p = 1.504 \text{ g mL}^{-1}$, 100 μL , 1.25 equiv.) and 7-methyl-1,5,7-triaza-bicyclo[4.4.0]-dec-5-ene [MTBD] **89** (71.4 mg, 0.46 mmol, $p = 1.067 \text{ g mL}^{-1}$, 70 μL , 1.26 equiv.) were combined, concentrated *in vacuo* affording the crude **365** as a yellow oil, which was used without further purification. No characterisation of **365** was attempted.

7.4.3 Wittig reactions with and without 4-nitrobenzoic acid (Lewis acid)**General procedure 9:**

A solution of diketone (1.0 equiv.), ylide (1-3 equiv.) and 4-nitrobenzoic acid (0.2-0.4 equiv.) [required] in different solvents like dichloromethane, anhydrous benzene and toluene (20 mL) was heated at reflux for 15 hours, the mixture was cooled to room temperature and then concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica using different eluents to afford the products. Conversion was determined by analysis of the ^1H -NMR spectrum.

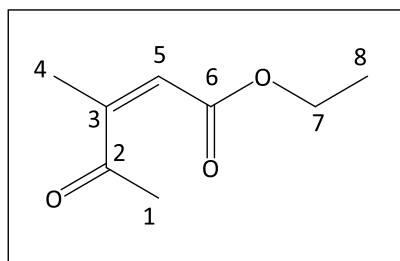
Attempted preparation of 3,4-dimethyl-hexadien-2,4-dinitril **390**:



According to **general procedure 9** using 2,3-butanedione **375** (50 mg, 0.58 mmol, $\rho = 0.981 \text{ g mL}^{-1}$, 50 μL , 1 equiv.), (triphenylphosphoranylidene)acetonitrile **265** (524 mg, 1.74 mmol, 3 equiv.) and 4-nitrobenzoic acid (0.2 or 0.4 equiv.) were combined. Concentration *in vacuo* afforded the crude **390** as faint yellow oil, which was used without further purification. No characterisation of **390** in both reactions was attempted.

Run	4-nitrobenzoic acid (Catalyst)			Solvent/ conditions /15 h	Yield %
	equiv.	mmol	mg		
1	-	-	-	Anhydrous benzene/rt	NR
2	0.2	0.116	19	Toluene/rt	Dec.
3	0.4	0.232	39	Toluene/reflux	NR

Preparation of (*E,Z*)-ethyl 3-methyl-4-oxo-2-pentenoate **376**:



Procedure A:

According to **general procedure 9** using 2,3-butanedione **375** (100 mg, 1.16 mmol, $\rho = 0.981 \text{ g mL}^{-1}$, 100 μL , 1 equiv.), ethyl

(triphenylphosphoranylidene)acetate **38** (401 mg, 1.375 mmol, 1 equiv.) in dichloromethane were combined, concentrated *in vacuo* affording the crude **367** as faint yellow oil (97 mg, 0.57 mmol, 100%). **376**: R_f = 0.59 (2.5:7.5 diethyl ether/hexane, det: KMnO_4); $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): δ = 1.33 (t, J = 7.2 Hz, 3H, H_8), 2.22 (d, J = 1.5 Hz, 3H, H_4), 2.40 (s, 3H, H_1), 4.25 (q, J = 7.2 Hz, 2H, H_7), 5.32 (1H, H_5 , (Z)-isomer), 6.59 (q, J = 1.4 Hz, 1H, H_5 , (E)-isomer); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 25 °C): δ = 13.0 (C4), 14.2 (C8), 26.8 (C1), 60.8 (C7), 126.6 (C5), 150.4 (C3), 166.2 (C6), 200.0 (C2); IR (neat): ν_{max} (cm^{-1}) = 1725, 1690, 1640; MS (ESI), 156 (MH^+), HRMS (ESI, $m/z\%$) calcd. for $\text{C}_8\text{H}_{13}\text{O}_3$ [$(\text{M}+\text{H})^+$]: 156.0864, found 156.0820, 1.5 ppm error.

Procedure B:

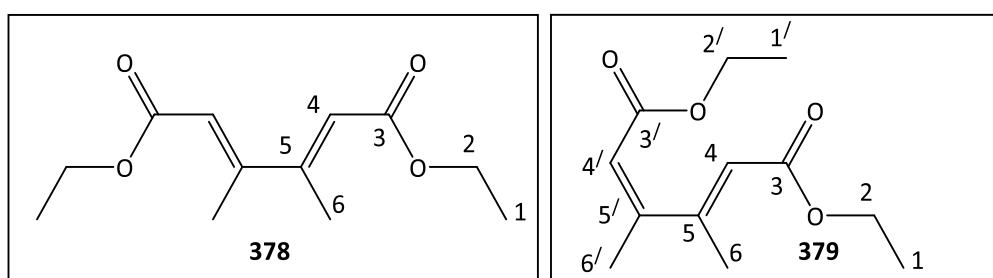
According to **general procedure 9** using 2,3-butanedione **375** (50 mg, 0.58 mmol, ρ = 0.981 g mL^{-1} , 50 μL , 1 equiv.), ethyl (triphenylphosphoranylidene)acetate **377** (341 mg, 1.74 mmol, 3 equiv.) and 7-methyl-1,5,7-triaza-bicyclo[4.4.0]dec-5-ene [MTBD] **89** (275 mg, 1.79 mmol, ρ = 1.067 g mL^{-1} , 250 μL , 3.1 equiv.) in toluene (20 mL) were combined, evaporated the solvent under higher vacuum affording the crude **376**, which was used without further purification. No characterisation of **376** was attempted (no reaction).

Procedure C:

According to **general procedure 9** using 2,3-butanedione **375** (100 mg, 1.16 mmol, ρ = 0.981 g mL^{-1} , 100 μL , 1 equiv.), ethyl (triphenylphosphoranylidene)acetate **38** (900 mg, 2.6 mmol, 2.2 equiv.) in anhydrous benzene (10 mL) were combined, evaporated the solvent under

higher vacuum affording the crude **376**, a 95:5 mixture of (*E*)/(*Z*) isomers, as a colourless oil (170 mg, 1.08 mmol, 94%). **376**: R_f = 0.61 [*E*], 0.44 [*Z*] (5:5 diethyl ether/hexane, det: KMnO_4); $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): (***E*** isomers δ = 1.33 (q, J = 7.2 Hz, 3H, H_8), 2.21 (d, J = 0.7 Hz, 3H, H_4), 2.40 (s, 3H, H_1), 4.25 (q, J = 7.1 Hz, 2H, H_7), 6.59 (s, 1H, H_5); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 25 °C): δ = 13.0 (C_4), 14.1 (C_8), 26.1 (C_1), 60.7 (C_7), 126.5 (C_5), 150.4 (C_3), 166.1 (C_6), 199.8 (C_2); MS (ESI), 156 (MH^+), HRMS (ESI+ $m/z\%$): calcd for $\text{C}_8\text{H}_{13}\text{O}_3$ [$\text{M}+\text{H}$] $^+$: 157.0864, found 156.0861, -1.43 ppm error; (***Z*** isomers δ = 1.25-1.29 (m, 3H, H_8), 1.99 (d, J = 0.7 Hz, 3H, H_4), 2.37 (d, J = 0.5 Hz, 3H, H_1), 4.16 (q, J = 7.0 Hz, 2H, H_7), 5.69 (d, J = 0.5 Hz 1H, H_5); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 25 °C): δ = 14.1 (C_8), 20.2 (C_4), 28.6 (C_1), 60.7 (C_7), 117.1 (C_5), 157.1 (C_3), 165.2 (C_6), 206.2 (C_2); IR (neat): ν_{max} (cm^{-1}) = 1725, 1690, 1640; MS (ESI), 156 (MH^+), HRMS (ESI, $m/z\%$) calcd. for $\text{C}_8\text{H}_{13}\text{O}_3$ [$\text{M}+\text{H}$] $^+$: 156.0864, found 156.0860, -1.44 ppm error.

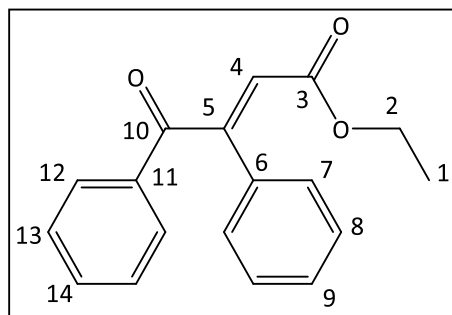
Preparation of diethyl (*E,E*) and (*E,Z*)-3,4-dimethylmuconate (378**) and (**379**):**



To a cooled 0 °C solution of sodium hydride (28.8 mg, 1.20 mmol, 1.94 equiv.) in anhydrous benzene (3 mL) under nitrogen pressure, followed by adding ethyl 2-(dimethoxyphosphoryl)acetate **38** (239 mg, 1.22 mmol, p = 1.186 g mL^{-1} , 200 μL , 1.97 equiv.). A solution of **376** (97 mg, 0.62 mmol, 1 equiv.) was added dropwise to the solution, stirred at room temperature for 15 hours, poured

into water (10 mL), extracted with diethyl ether (50 mL) and dried (MgSO_4). The filtrate was concentrated under higher vacuum affording the crude **378** and **379**, a 95:5 mixture of (*E,E*)/(*E,Z*) isomers, as a yellow oil (130 mg, 0.57 mmol, 92.8%). **378** and **379**: R_f = 0.50 [*E,E*], 0.25 [*E,Z*] (0.5:9.5 diethyl ether/hexane, det: KMnO_4); $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): (***E,E***) isomers δ = 1.30 (q, J = 7.1 Hz, 3H, H_1), 2.32 (s, 3H, H_6), 4.19 (q, J = 7.1 Hz, 2H, H_2), 6.04 (s, 2H, H_4); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 25 °C): δ = 14.2 (C_1), 15.8 (C_6), 60.1 (C_2), 118.9 (C_4), 155.3 (C_5), 166.5 (C_3); MS (ESI), 227 (MH^+), HRMS (ESI, $m/z\%$) calcd. for $\text{C}_{12}\text{H}_{19}\text{O}_4$ [$(\text{M}+\text{H})^+$]: 227.1283, found 227.1282, -1.69 ppm error; (***E,Z***) isomers δ = 1.22-1.26 (m, 3H, H_1), 1.28 (t, J = 7.5 Hz, 3H, H_1'), 1.98 (s, 3H, H_6), 2.32 (d, J = 0.5 Hz, 3H, H_6'), 4.10-4.14 (m, 3H, H_2), 4.14-4.19 (m, 2H, H_2'), 5.56 (s, 1H, H_4), 5.64 (s, 1H, H_4'); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 25 °C): δ = 14.1 (C_1), 14.3 (C_1'), 17.9 (C_6), 24.5 (C_6'), 59.8 (C_2), 60.1 (C_2'), 115.4 (C_4), 116.6 (C_4'), 157.6 (C_5), 158.3 (C_5'), 165.1 (C_3), 166.3 (C_3'); MS (ESI), 227 (MH^+), HRMS (ESI, $m/z\%$) calcd. for $\text{C}_{12}\text{H}_{19}\text{O}_4$ [$(\text{M}+\text{H})^+$]: 227.1283, found 227.1285, -3.34 ppm error.

Preparation of 4-oxo-3,4-phenylbut-2-enoic acid ethyl ester **421**:



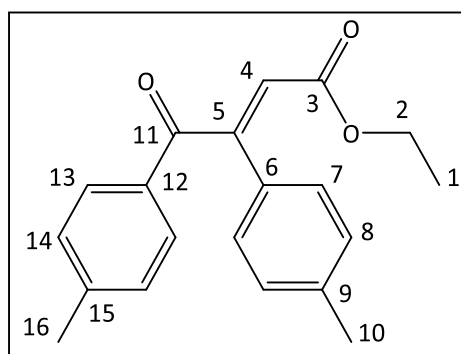
According to **general procedure 9** using benzil **318** (50 mg, 0.23 mmol, 1 equiv.), ethyl (triphenylphosphoranylidene)acetate **38** (200 mg, 0.575 mmol,

2.5 equiv.) in toluene (25 mL) were combined, concentrated *in vacuo*, purified twice by flash chromatography on silica gel using 3:7 ethyl acetate/hexane as the eluent affording the crude **421** as faint yellow oil (20 mg, 0.06 mmol, 31%).

421:⁽²²⁹⁾ R_f = 0.5 (PTLC, 3:7 diethyl ether/hexane, det: KMnO_4); $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): δ = 1.10-1.16 (m, 3H, H_1), 4.02-4.15 (m, 2H, H_2), 6.26 (s, 1H, H_4), 7.36-7.39 (m, 5H, $\text{H}_7, \text{H}_8, \text{H}_9$), 7.46-7.48 (m, 2H, H_{12}), 7.55-7.58 (m, 1H, H_{14}), 7.91-7.95 (m, 2H, H_{13}); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 25 °C): δ = 13.9 (C1), 60.9 (C2), 124.0 (C4), 128.2 (C7), 128.5 (C8), 128.7 (C9), 128.9 (C12), 130.1 (C13), 133.7 (C14), 134.3 (C6), 135.7 (C11), 152.2 (C5), 165.4 (C3), 195.7 (C10); IR (neat): ν_{max} (cm^{-1}) = 2998, 2943, 1713, 1669, 1448, 1375, 1254, 1203, 1066, 918, 812, 737, 677; MS (ESI), 281 (MH^+), HRMS (ESI, $m/z\%$) calcd. for $\text{C}_{18}\text{H}_{17}\text{O}_3$ [$(\text{M}+\text{H})^+$]: 281.1177, found 281.1178, -1.83 ppm error.

No effect was noticed when 4-nitrobenzoic acid (15 mg, 0.09 mmol, 0.4 equiv.) added to the reaction under the same conditions above.

Preparation of 4-oxo-3,4-tolylbut-2-enoic acid ethyl ester **382**:



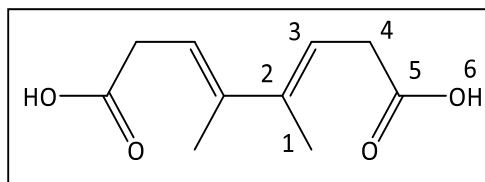
Procedure A:

According to **general procedure 9** using 1,2-di(4-methylphenyl)-1,2-ethanedione **371** (50 mg, 0.2 mmol, 1 equiv.), ethyl

(triphenylphosphoranylidene)acetate **38** (174 mg, 0.5 mmol, 2.5 equiv.) and 4-nitrobenzoic acid (13.3 mg, 0.08 mmol, 0.4 equiv.) in toluene (20 mL) were combined, concentrated *in vacuo* affording the crude **382** as faint yellow oil (22 mg, 0.07 mmol, 34%). **382**: R_f = 0.60 (7:3 petroleum ether (b.p 40-60 °C) /ethyl acetate, det: KMnO₄).

Procedure B:

According to **general procedure 9** using 1,2-di(4-methylphenyl)-1,2-ethanedione **371** (100 mg, 0.42 mmol, 1 equiv.), ethyl (triphenylphosphoranylidene)acetate **38** (320 mg, 0.924 mmol, 2.2 equiv.) in anhydrous benzene were combined, concentrated *in vacuo* affording the **382** product as faint yellow oil (90 mg, 0.29 mmol, 70%). **382**: R_f = 0.50 (5:5 diethyl ether/hexane, det: KMnO₄); ¹H-NMR (300 MHz, CDCl₃, 25 °C): δ = 1.17 (t, J = 7.0 Hz, 3H, H₁), 2.34 (s, 3H, H₁₀), 2.40 (s, 3H, H₁₆), 4.14 (q, J = 6.7 Hz, 2H, H₂), 6.17 (s, 1H, H₄), 7.24 (d, J = 7.6 Hz, 2H, H₈), 7.30 (d, J = 7.6 Hz, 2H, H₁₄), 7.82 (d, J = 7.3 Hz, 2H, H₇), 7.86 (d, J = 7.3 Hz, 2H, H₁₃); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): δ = 14.0 (C1), 21.4 (C10), 21.7 (C16), 60.7 (C2), 122.4 (C4), 129.3 (C8), 129.7 (C14), 130.0 (C13), 130.3 (C7), 133.2 (C9), 139.0 (C15), 144.6 (C6), 146.1 (C12), 152.8 (C5), 165.5 (C3), 194.5 (C11); IR (neat): ν_{\max} (cm⁻¹) = 2988, 2970, 2901, 1724, 1663, 1373, 1252, 1066, 9018, 818, 737, 731, 708; MS (ESI), 309 (MH⁺), HRMS (ESI, m/z%) calcd. for C₂₀H₂₁O₃ [(M+H)⁺]: 309.1490, found 309.1492, – 2.32 ppm error.

Attempted preparation of 4,5-dimethylocta-3,5-dienedioic acid **385:****Procedure A:**⁽²³⁰⁾

A mixture of 2,3-butanedione **375** (100 mg, 1.16 mmol, $p = 0.981 \text{ g mL}^{-1}$, 100 μL , 1 equiv.) in triethylamine (3 mL), malonic acid **384** (241 mg, 2.32 mmol, 2 equiv.) was added. The resulted mixture was stirred and heated at 98 °C for an hour. After the mixture had been cooled to room temperature, the solution was poured into 10% ice hydrochloric acid solution (10 mL), extracted with diethyl ether (10 mL), washed with 5% sodium hydroxide solution (10 mL). The aqueous layer was extracted with diethyl ether (10 mL), washed with 10% hydrochloric acid solution (10 mL), and then extracted further with diethyl ether (10 mL). The extract was washed with brine (10 mL), dried (MgSO_4), and concentrated *in vacuo* affording the crude **385** as white solid, which was used without further purification. No characterisation of **385** was attempted.

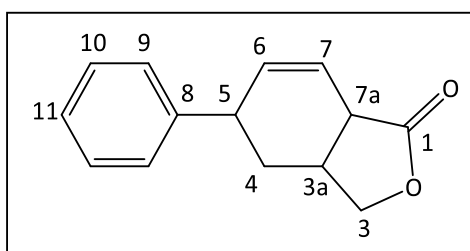
Procedure B:⁽²³¹⁾

To a stirred solution of malonic acid **384** (241 mg, 2.32 mmol, 2 equiv.) and triethylamine (305 mg, 3.01 mmol, $p = 0.726 \text{ g mL}^{-1}$, 420 μL , 2.6 equiv.) in toluene (10 mL), a solution of 2,3-butanedione **375** (100 mg, 1.16 mmol, $p = 0.981 \text{ g mL}^{-1}$, 100 μL , 1 equiv.) in piperidine (35.5 mg, 0.417 mmol, $p = 0.862 \text{ g mL}^{-1}$, 40 μL , 0.36 equiv.) was added. The resulted mixture was stirred and heated at 70°C for overnight. After the mixture had been cooled to room

temperature, the solution was extracted with 5 mL of 5% saturated sodium bicarbonate solution for 10 min., and then washed with 10 mL of ethyl acetate. The aqueous layer was cooled the acidified with drops of 10% hydrochloric acid solution until white solid precipitated. The solid was filtered and dried under higher vacuum to afford the crude **385** as white solid, which was used without further purification. No characterisation of **385** was attempted.

7.4.4 Attempts of Diels-Alder reactions

Attempted preparation of 5-phenyl-3,3a,4,5,7a-hexahydroisobenzofuran-1-one 355:



Procedure A:

Allyl (triphenylphosphoranylidene) acetate **354** (20 mg, 0.05 mmol, 1.0 equiv.) was dissolved in xylene (10 mL) or mesitylene (10 mL). To the solution was added hydroquinone (270 mg, 2 mmol, 0.05 equiv.) and heated at reflux for overnight. The reaction mixture was concentrated *in vacuo* to give the crude product as thick oil, which was used without further purification. No characterisation of **355** was attempted.

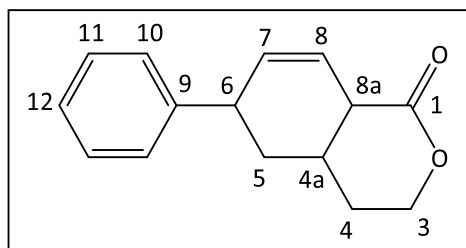
Procedure B:

A solution of allyl (triphenylphosphoranylidene) acetate **354** (41 mg, 0.113 mmol, 1 equiv.) in diphenyl ether (7 mL) was stirred and heated at reflux for overnight, and then concentrated *in vacuo*. A 50 g of silica gel was weighed in prepared column, added petroleum ether (100 mL), and then added the reaction after dissolving with petroleum ether (100 mL) through this column, and washed with ethyl acetate (50 mL). The collected crude was concentrated *in vacuo*, which was used without further purification. No characterisation of **355** was attempted.

Procedure C:

To a solution of allyl (triphenylphosphoranylidene) acetate **354** (20 mg, 0.05 mmol, 1 equiv.) in anhydrous benzene (10 mL) was added lithium tetrafluoroborate solution [1.0 M in MeCN] (60 μ L, 0.06 mmol, 1.1 equiv.), stirred and heated at reflux. After 15 hours, the reaction mixture was washed with dichloromethane (50 mL). The dichloromethane layer was extracted with water (50 mL), dried (MgSO₄), filtered, and concentrated *in vacuo* to afford the crude as yellow oil, which was used without further purification. No characterisation of **355** was attempted.

Attempted preparation of 6-phenyl-3,4,4a,5,6,8a-hexahydro-1H-2-benzopyran-1-one **366**:



Procedure A:

To a solution of 3'-butyen-1'-yl 2-(triphenylphosphoranylidene)acetate **364** (30 mg, 0.08 mmol, 1 equiv.) in toluene (10 mL) was added bismuth(III) triflate (57 mg, 0.087 mmol, 1.1 equiv.) or *p*-toluenesulfonic acid monohydrate (16.5 mg, 0.087 mmol, 1.1 equiv.) or triflic acid (12.7 mg, 0.087 mmol, $p = 1.696 \text{ g mL}^{-1}$, 7 μL , 1.1 equiv.), stirred and heated at reflux for overnight. After this time, the reaction mixture was quenched with saturated sodium bicarbonate solution (20 mL), extracted with dichloromethane (15 mL). The extract was washed with brine (30 mL), dried (MgSO_4), filtered, and concentrated *in vacuo* to afford the crude as yellow oil, which was used without further purification. No characterisation of **366** was attempted.

Procedure B:

A solution of 3'-butyen-1'-yl-2-(triphenylphosphoranylidene)acetate **364** (48 mg, 0.127 mmol, 1 equiv.) in diphenyl ether (7 mL) was stirred and heated at reflux for 15 hours, and then concentrated *in vacuo*. A 50 g of silica gel was weighed in prepared column, added petroleum ether (100 mL), and then added the reaction after dissolving with petroleum ether (100 mL) through this

column, and washed with ethyl acetate (50 mL). The collected crude was concentrated *in vacuo*, which was used without further purification. No characterisation of **366** was attempted.

Procedure C:

To a solution of 3'-butyen-1'-yl-2-(triphenylphosphoranylidene)acetate **364** (20 mg, 0.053 mmol, 1 equiv.) in anhydrous benzene (10 mL) was added lithium tetrafluoroborate solution [1.0 M in MeCN] (53 μ L, 0.053 mmol, 1.1 equiv.), stirred and heated at reflux. After 15 hours, the reaction mixture was washed with dichloromethane (50 mL). The dichloromethane layer was extracted with water (50 mL), dried (MgSO₄), filtered, and concentrated *in vacuo* to afford the crude as yellow oil, which was used without further purification. No characterisation of **366** was attempted.

7.4.5 TOP reactions using different oxidants

General procedure 10: TOP for the preparation of dienes with SO₃Py

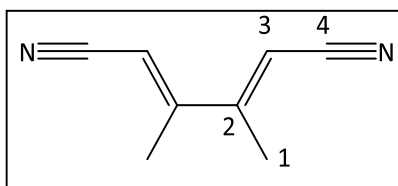
To a solution of diol (1 equiv.), ylides (2.5 equiv.) and triethylamine (20 equiv.) was dissolved in dichloromethane (1 mL) at 0 °C and then treated with a solution of pyridine sulfur trioxide complex (10 equiv.) in dichloromethane (2 mL) and DMSO (3 mL), stirred for 16 hours at room temperature and 50 °C, poured into water (50 mL) and extracted with dichloromethane (4 × 100 mL). The extracts were washed sequentially with saturated brine (20 mL), dried (MgSO₄), and filtered through a pad of celite, concentrated to provide the product of sufficient purity for subsequent use with further purification.

General procedure 11: TOP for the preparation of dienes with iodoxybenzoic acid (IBX)

To a cooled 0 °C solution of diol (1 equiv.) and ylides (2.5 equiv.) was dissolved in dichloromethane (5 mL), and a solution of IBX (20 equiv.) in DMSO (3 equiv.) was added slowly, stirred for 2 hours at room temperature. This resultant solution was filtered through celite, extracted with diethyl ether (50 mL), washed sequentially with water (20 mL), saturated brine (20 mL), dried (MgSO₄), concentrated *in vacuo* to afford the crude product. Conversion was determined by analysis of the ¹H-NMR spectrum.

General procedure 12: TOP for the preparation of dienes with Dess-Martin periodinane (DMP)

Diol (1 equiv.) and ylide (2.5 equiv.) were dissolved in anhydrous dichloromethane or toluene (10 mL). Dess-Martin periodinane (3 equiv.) was added, and the mixture turned orange-red brown within seconds. The resultant solution was stirred at room temperature for three hours, followed by a further 15 hours at 90 °C. The crude was extracted with diethyl ether (50 mL) and washed with saturated NaHCO₃ solution (50 mL). After stirring for an hour, the mixture was filtered, separated. The organic layer was dried (MgSO₄) and concentrated *in vacuo*. The crude was used in the next step. Conversion was determined by analysis of the ¹H-NMR spectrum.

Attempted preparation of 3,4-dimethyl-hexadien-2,4-dinitril 390:**Procedure A:**

According to **general procedure 10** using 2,3-butanediol **350** (50 mg, 0.55 mmol, $\rho = 1.002 \text{ g mL}^{-1}$, 50 μL , 1 equiv.), triethylamine (1.11 g, 11 mmol, $\rho = 0.727 \text{ g mL}^{-1}$, 1.53 mL, 20 equiv.), (triphenylphosphoranylidene)acetonitrile **265** (414 mg, 1.375 mmol, 2.5 equiv.) and pyridine sulfur trioxide complex (873 mg, 1.43 mmol, 10 equiv.) were combined. Concentration *in vacuo* afforded the crude **390** as faint yellow oil. No characterisation of **390** was attempted (no reaction).

According to **general procedure 10** using 2,3-butanediol **350** (50 mg, 0.55 mmol, $\rho = 1.002 \text{ g mL}^{-1}$, 50 μL , 1 equiv.), triethylamine (1.11 g, 11 mmol, $\rho = 0.727 \text{ g mL}^{-1}$, 1.53 mL, 20 equiv.), diethyl 1-cyano-methylphosphonate **420** (243 mg, 1.375 mmol, $\rho = 1.095 \text{ g mL}^{-1}$, 220 μL , 2.5 equiv.) and 7-methyl-1,5,7-triazabicyclo[4.4.0]-dec-5-ene [MTBD] **89** (219 mg, 1.43 mmol, $\rho = 1.067 \text{ g mL}^{-1}$, 70 μL , 2.6 equiv.) and pyridine sulfur trioxide complex (873 mg, 5.5 mmol, 10 equiv.) were combined. No characterisation of **390** was attempted.

Procedure B:

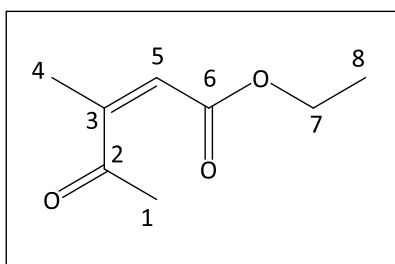
According to **general procedure 11** using 2,3-butanediol **350** (50 mg, 0.55 mmol, $\rho = 1.002 \text{ g mL}^{-1}$, 50 μL , 1 equiv.), Iodoxybenzoic acid (231 mg, 0.825 mmol, 1.5 equiv.), (triphenylphosphoranylidene)acetonitrile **265** (414 mg, 1.375 mmol, 2.5 equiv.) and DMSO (128 mg, 1.65 mmol, $\rho = 1.1 \text{ g mL}^{-1}$, 110 μL ,

3 equiv.) were combined. Concentration *in vacuo* afforded the crude **390** as red oil. No characterisation of **390** was attempted.

Procedure C:

According to **general procedure 12** using 2,3-butanediol **350** (50 mg, 0.55 mmol, $\rho = 1.002 \text{ g mL}^{-1}$, 50 μL , 1 equiv.), DMP (699 mg, 1.65 mmol, 3 equiv.), (triphenylphosphoranylidene)acetonitrile **265** (414 mg, 1.375 mmol, 2.5 equiv.) were combined. Concentration *in vacuo* afforded the crude **390** as faint yellow oil. No characterisation of **390** was attempted.

Preparation of (*E*)-ethyl 3-methyl-4-oxo-2-pentenoate **376:**



Procedure A:

According to **general procedure 10** using 2,3-butanediol **350** (50 mg, 0.55 mmol, $\rho = 1.002 \text{ g mL}^{-1}$, 50 μL , 1 equiv.), triethylamine (1.11 g, 11 mmol, $\rho = 0.727 \text{ g mL}^{-1}$, 1.53 mL, 20 equiv.), ethyl (triphenylphosphoranylidene)acetate **38** (479 mg, 1.375 mmol, 2.5 equiv.) and pyridine sulfur trioxide complex (873 mg, 5.5 mmol, 10 equiv.) were combined to give the product as a yellow oil. No characterisation of **376** was attempted (no reaction).

According to **general procedure 10** using 2,3-butanediol **350** (50 mg, 0.55 mmol, $\rho = 1.002 \text{ g mL}^{-1}$, 50 μL , 1 equiv.), triethylamine (1.11 g, 11 mmol, $\rho = 0.727 \text{ g mL}^{-1}$, 1.53 mL, 20 equiv.), ethyl 2-(dimethoxyphosphoryl)acetate **381** (269 mg, 1.375 mmol, $\rho = 1.186 \text{ g mL}^{-1}$, 220 μL , 2.5 equiv.) and 7-methyl-1,5,7-

triazabicyclo[4.4.0]-dec-5-ene [MTBD] **89** (219 mg, 1.43 mmol, $\rho = 1.067 \text{ g mL}^{-1}$, 70 μL , 2.6 equiv.) and pyridine sulfur trioxide complex (873 mg, 5.5 mmol, 10 equiv.) were combined, concentrated under higher vacuum affording the crude **376** as faint yellow oil. No characterisation of **376** was attempted.

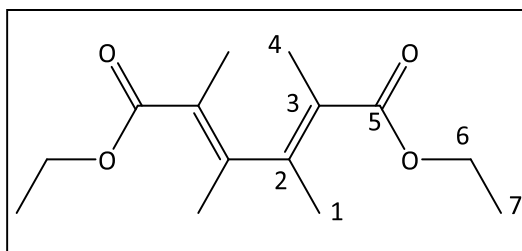
Procedure B:

According to **general procedure 11** using 2,3-butanediol **350** (50 mg, 0.55 mmol, $\rho = 1.002 \text{ g mL}^{-1}$, 50 μL , 1 equiv.), IBX (385 mg, 1.375 mmol, 2.5 equiv.), ethyl (triphenylphosphoranylidene)acetate **38** (479 mg, 1.375 mmol, 2.5 equiv.) and in DMSO (6 mL) were combined to give the product as red oil. No characterisation of **376** was attempted.

Procedure C:

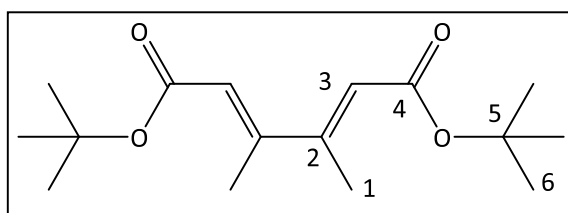
According to **general procedure 12** using 2,3-butanediol **350** (50 mg, 0.55 mmol, $\rho = 1.002 \text{ g mL}^{-1}$, 50 μL , 1 equiv.), DMP (699 mg, 1.65 mmol, 3 equiv.), ethyl (triphenylphosphoranylidene)acetate **38** (479 mg, 1.375 mmol, 2.5 equiv.) in toluene were combined, concentration *in vacuo* afforded the alkene product **376** as faint yellow oil (10 mg, 0.064 mmol, 11%). **376**: $R_f = 0.70$ (7:3 petroleum ether (b.p. 40-60 °C)/ethyl acetate, det: KMnO_4); $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): $\delta = 1.31\text{-}1.36$ (m, 3H, H_8), 2.22 (d, $J = 1.3 \text{ Hz}$, 3H, H_4), 2.40 (s, 3H, H_1), 4.24 (q, $J = 7.2 \text{ Hz}$, 2H, H_7), 6.59 (q, $J = 1.4 \text{ Hz}$, 1H, H_5); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 25 °C): $\delta = 13.0$ (C4), 14.2 (C8), 26.8 (C1), 60.8 (C7), 126.6 (C5), 150.4 (C3), 166.2 (C6), 200.0 (C2); IR (neat): $\nu_{\text{max}} (\text{cm}^{-1}) = 1725, 1690, 1640$; MS (ESI), 156 (MH^+), HRMS (ESI, $m/z\%$) calcd. for $\text{C}_8\text{H}_{13}\text{O}_3$ [$(\text{M}+\text{H})^+$]: 156.0864, found 156.0820, 1.5 ppm error.

Attempted preparation of 1,3-dimethyl-4-dimethyl-1,4-dicarboethoxy-1,3-butadiene 392:

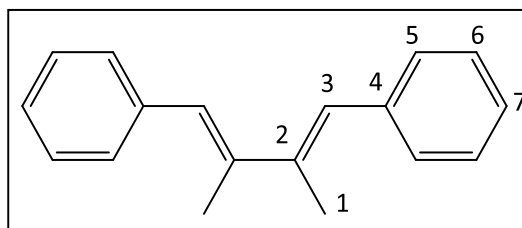


According to **general procedure 12** using 2,3-butanediol **350** (50 mg, 0.55 mmol, $\rho = 1.002 \text{ g mL}^{-1}$, 50 μL , 1 equiv.), DMP (699 mg, 1.65 mmol, 3 equiv.) and (carbethoxyethylidene)triphenylphosphorane **35** (498g, 1.375 mmol, 2.5 equiv.) were combined. Concentration *in vacuo* afforded the crude **392** as yellow oil. No characterisation of **392** was attempted.

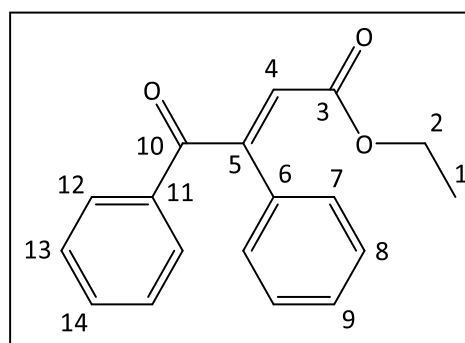
Attempted preparation 1,4-ditertbutyl ester-2,3-dimethyl-1,3-butadiene 394:



According to **general procedure 12** using 2,3-butanediol **350** (50 mg, 0.55 mmol, $\rho = 1.002 \text{ g mL}^{-1}$, 50 μL , 1 equiv.), DMP (699 mg, 1.65 mmol, 3 equiv.) and (*tert*-butoxycarbonylmethylene)triphenylphosphorane **304** (517 g, 1.375 mmol, 2.5 equiv.) were combined, concentrated *in vacuo* afforded the crude **394** as yellow oil. No characterisation of **394** was attempted.

Attempted preparation of 1,4-diphenyl-2,3-dimethyl-1,3-butadiene 396:

According to **general procedure 12** using 2,3-butanediol **350** (50 mg, 0.55 mmol, $\rho = 1.002 \text{ g mL}^{-1}$, 50 μL , 1 equiv.), DMP (699 mg, 1.65 mmol, 3 equiv.), benzyltriphenylphosphonium bromide **316** (595 mg, 1.375 mmol, 2.5 equiv.) and 7-methyl-1,5,7-triaza-bicyclo[4.4.0]dec-5-ene [MTBD] **89** (219 mg, 1.43 mmol, $\rho = 1.067 \text{ g mL}^{-1}$, 200 μL , 2.6 equiv.) were combined, concentration *in vacuo* afforded the crude **396** as yellow oil. No characterisation of **396** was attempted.

Preparation of 4-oxo-3,4-diphenylbut-2-enoic acid ethyl ester 421:**Procedure A:**

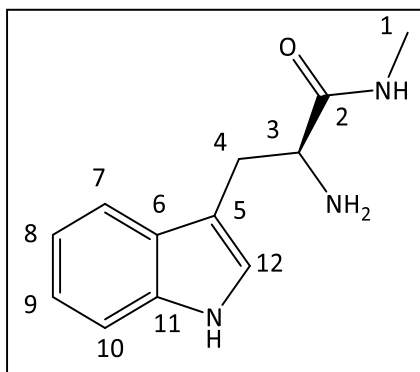
According to **general procedure 10** using hydrobenzoin **368** (50 mg, 0.23 mmol, 1 equiv.), triethylamine (465 mg, 4.6 mmol, $\rho = 0.727 \text{ g mL}^{-1}$, 640 μL , 20 equiv.), ethyl (triphenylphosphoranylidene)acetate **38** (200 mg, 0.575 mmol, 2.5 equiv.) and pyridine sulfur trioxide complex (366 mg, 2.3 mmol, 10 equiv.) were combined affording the product as yellow oil (39 mg, 0.14 mmol, 60%).

421:⁽²²⁹⁾ R_f = 0.60 (7:3 hexane/ diethyl ether, det: KMnO_4); $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): δ = 1.10-1.16 (m, 3H, H_1), 4.02-4.15 (m, 2H, H_2), 6.26 (s, 1H, H_4), 7.36-7.39 (m, 5H, H_7 , H_8 , H_9), 7.46-7.48 (m, 2H, H_{12}), 7.55-7.58 (m, 1H, H_{14}), 7.91-7.95 (m, 2H, H_{13}); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 25 °C): δ = 13.9 (C_1), 60.9 (C_2), 124.0 (C_4), 128.2 (C_7), 128.5 (C_8), 128.7 (C_9), 128.9 (C_{12}), 130.1 (C_{13}), 133.7 (C_{14}), 134.3 (C_6), 135.7 (C_{11}), 152.2 (C_5), 165.4 (C_3), 195.7 (C_{10}); IR (neat): ν_{max} (cm^{-1}) = 2998, 2943, 1713, 1669, 1448, 1375, 1254, 1066, 1025, 918, 812, 737, 677; MS (ESI), 281 (MH^+), HRMS (ESI, $m/z\%$) calcd. for $\text{C}_{18}\text{H}_{17}\text{O}_3$ [$(\text{M}+\text{H})^+$]: 281.1177, found 281.1178, -1.83 ppm error.

Procedure B:

According to **general procedure 11** using hydrobenzoin **368** (50 mg, 0.23 mmol, 1 equiv.), IBX (161 mg, 0.575 mmol, 2.5 equiv.), ethyl (triphenylphosphoranylidene)-acetate **38** (200 mg, 0.575 mmol, 2.5 equiv.) in DMSO (6 mL) were combined, concentrated *in vacuo* to afford the crude as red oil. No characterisation of **421** was attempted (no reaction).

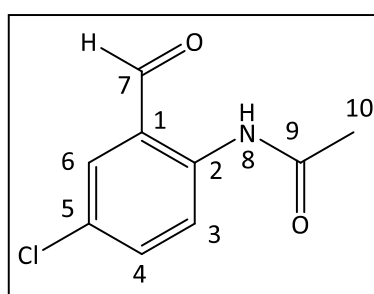
7.5 Experimental procedures: Chapter 5

Preparation of (S)-2-amin-3-(1H-indol-3-yl)-N-methylpropanamide **432**:**Procedure A:**

Methylamine **431a** (40 ml, 2.0 M in THF, 20 equiv.) was added to a suspension of L-tryptophan methyl ester hydrochloride **430** (500 mg, 1.96 mmol, 1 equiv.) in THF (10 ml) and then stirred at room temperature. After 24 h, the solvent was evaporated *in vacuo*, and the crude was purified by column chromatography 20% methanol/dichloromethane to give the product as a yellow solid (150 mg, 35%). **432**:⁽¹⁹²⁾; R_f = 0.57 (8:2 dichloromethane/methanol, det: KMnO_4); m.p. 120-122 °C; $^1\text{H-NMR}$ (300 MHz, CD_3OD , 25 °C): δ = 3.12 (s, 3H, H_1), 2.94-3.01 (m, 1H, H_{4a}), 3.11-3.18 (m, 1H, H_{4b}), 3.54-3.59 (m, 1H, H_3), 6.97-7.03 (m, 1H, H_8), 7.07 (s, 1H, H_{12}), 7.08-7.11 (m, 1H, H_9), 7.33 (dt, J = 8.1, 1, 1H, H_{10}), 7.57 (dt, J = 7.7, 1.1 Hz, 1H, H_7); $^{13}\text{C-NMR}$ (75 MHz, CD_3OD , 25 °C): δ = 26.3 (C_1), 32.2 (C_4), 56.9 (C_3), 111.2 (C_5), 112.3 (C_8), 119.5 (C_{10}), 119.8 (C_7), 122.5 (C_{12}), 124.7 (C_9), 128.8 (C_6), 138.2 (C_{11}), 17.7 (C_2); IR (NaCl disk): ν_{max} (cm^{-1}) = 3282, 1650, 1537, 1457, 1411, 1342, 1232, 1101; MS (ESI), 218 (MH^+), HRMS (ESI, m/z %) calcd. for $\text{C}_{12}\text{H}_{16}\text{N}_3\text{O}$ [$(\text{M}+\text{H})^+$]: 218.1293; found: 218.1295, – 4.1 ppm error.

Procedure B:

L-tryptophan **144** (4.85 g, 23.8 mmol, 1 equiv.) was added to a cooled solution of thionyl chloride (8.15 g, 67 mmol, $\rho = 1.631 \text{ g mL}^{-1}$, 5 mL, 2.8 equiv.) in methanol (130 mL) at 0 °C. The solution was stirred for 24 hours at room temperature then evaporated by *vacuo*. The crude reaction was washed with ethyl acetate (200 mL) and petroleum ether (100 mL). the solid was concentrated to afford a white solid. This solid was stirred at room temperature in an ethanolic solution of methylamine **431** (35 mL [33% in EtOH], 12 equiv.) for 4 days then evaporated, washed with saturated sodium bicarbonate solution (100 mL). The aqueous layer was extracted with chloroform (4 × 10 mL), and then chloroform extracts were combined to dry over (MgSO₄). The filtrate was evaporated to give the product **432**, as a yellow solid (4.5 g, 21 mmol, 87%). **432**: $R_f = 0.60$ (8:2 CH₂Cl₂/MeOH, det: KMnO₄). Data as recorded above in procedure A.

Preparation of 2-acetamino-5-chlorobenzaldehyde 452:

To a solution of 2-amino-5-chlorobenzaldehyde **451** (500 mg, 3.21 mmol, 1 equiv.) in pyridine (5 mL) under N₂ pressure, acetic anhydride (5.4 g, 52.8 mmol, $\rho = 1.08 \text{ g mL}^{-1}$, 5 mL, 16 equiv.) was added dropwise, then stirred at room temperature overnight. The resulted solution was concentrated *in vacuo*, and re-dissolved in dichloromethane (20 mL). Further evaporated the solution

in vacuo was required twice. The crude was extracted with dichloromethane (20 mL) and water (20 mL), washed with 2 M hydrochloric acid (20 mL) and then saturated sodium bicarbonate (5 mL). The organic layer was washed with saturated brine (20 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue *via* flash chromatography on silica using 9.5:0.5 dichloromethane/diethyl ether to afford the product as a thick yellow oil (470 mg, 2.4 mmol, 75%). **452**: R_f = 0.56 (9.5:0.5 dichloromethane/diethyl ether, det: KMnO₄); ¹H-NMR (300 MHz, CDCl₃, 25 °C): δ = 2.24 (s, 1H, H₁₀), 7.61 (d, *J* = 18.6 Hz, 2H, H₃, H₄), 8.73 (s, 1H, H₈), 9.84 (d, *J* = 18.1 Hz, 1H, H₆), 11.01 (s, 1H, H₇); ¹³C-NMR (75 MHz, CDCl₃, 25 °C): δ = 25.4 (C₁₀), 121.5 (C₆), 122.4 (C₅), 127.9 (C₂), 135.0 (C₃), 136.0 (C₄), 139.4 (C₁), 169.6 (C₉), 194.4 (C₇); MS (ESI), 198 (MH⁺), HRMS (ESI, *m/z* %) calcd. for C₉H₉³⁵ClNO₂ [(M+H)⁺]: 198.0321; found: 198.0323, −4.92 ppm error.

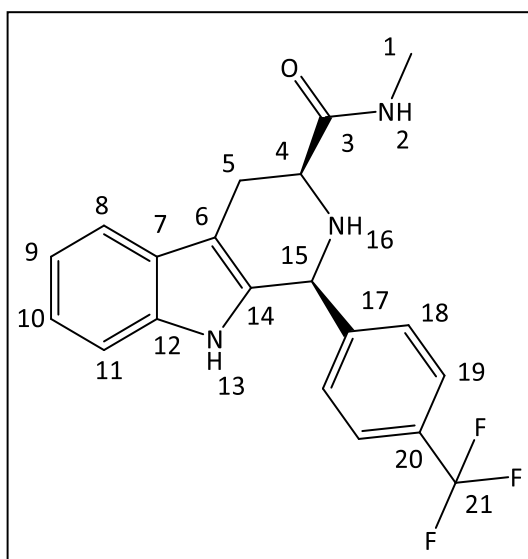
7.5.1 Pictet spengler reaction

General Procedure 13:

L-Trp-NHMe **432** (1 equiv.) was dissolved in anhydrous dichloromethane (20 mL) and 3 Å molecular sieves (10 mg) were placed under atmosphere of nitrogen and the aldehyde (1.1 equiv.) was added *via* cannula over a period of 5 min or a anhydrous dichloromethane solution if it is solid. The mixture was left the stir overnight to allow the imine to form. Trifluoroacetic acid (2 equiv.) was added *via* needle and the solution stirred for further three hours at room temperature. Saturated aqueous sodium bicarbonate (20 mL) was added to quench the reaction. The layers were separated and the aqueous layer was

further extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with saturated brine (20 mL), dried (MgSO₄), filtered and solvent evaporated *in vacuo*. The crude was purified by column chromatography.

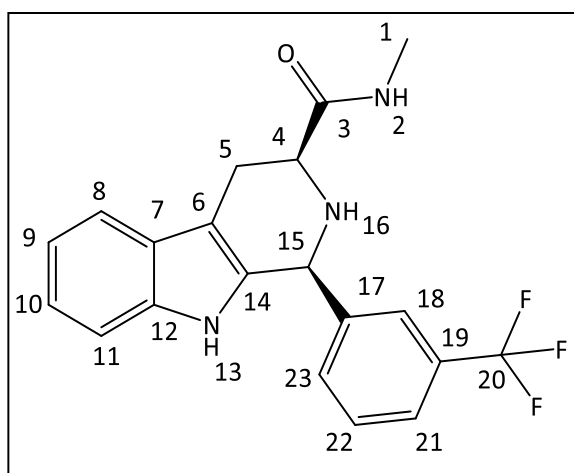
Preparation of (1S,3S)-1-([4-trifluoromethyl]phenyl)-3-acetamide-1,2,3,4-tetrahydro- β -carboline 436:



According to **general procedure 13** L-Trp-NHMe **432** (390 mg, 1.79 mmol, 1 equiv.), 3 Å molecular sieves (10 mg), 4-(trifluoromethyl)benzaldehyde **435** (342 mg, 1.96 mmol, $p = 1.275 \text{ g mL}^{-1}$, 260 μL , 1.1 equiv.) and trifluoroacetic acid (408 mg, 3.58 mmol, $p = 1.478 \text{ g mL}^{-1}$, 270 μL , 2 equiv.) were combined to afford white solid (90 mg, 0.24 mmol, 13%). **436**: $R_f = 0.55$ (7:3 dichloromethane/diethyl ether, det: KMnO₄); m.p. 192-194 °C; ¹H-NMR (300 MHz, CDCl₃, 25 °C): $\delta = 1.79$ (br.s, 1H, H₂), 2.82 (d, $J = 5.1 \text{ Hz}$, 3H, H₁), 2.83-2.86 (m, 1H, H_{5a}), 3.37 (ddd, $J = 15.6, 4.2, 1.8 \text{ Hz}$, 1H, H_{5b}), 3.72 (dd, $J = 11.1, 4.3 \text{ Hz}$, 1H, H₄), 5.25 (s, 1H, H₁₅), 7.10-7.19 (m, 2H, H₉, H₁₀), 7.22-7.24 (m, 1H, H₁₁), 7.45

(d, $J = 8.1\text{ Hz}$, 2H, H_{19} , H_{22}), 7.55 (dd, $J = 6.1$, 2.0 Hz, 1H, H_8), 7.62-7.65 (m, 3H, H_{18} , H_{23} , H_{13}). ^{13}C -NMR (75 MHz, CDCl_3 , 25 °C): $\delta = 25.6$ (C1), 25.9 (C5), 58.1 (C15), 110.5 (C6), 111.1 (C11), 118.5 (C8), 119.9 (C9), 122.4 (C10), 126.0 (q, $J = 3.8$ Hz) (C19, C22), 127.0 (C21), 129.0 (C18, C23), 130.7 (C7), 131.1 (C14), 133.3 (C20), 136.3 (C12), 144.7 (C17), 173.0 (C3); IR (neat): ν_{max} (cm^{-1}) = 2972, 1661, 1608, 1584, 1460, 739, 687; MS (ESI), 374 (MH^+), HRMS (ESI, m/z %) calcd. for $\text{C}_{20}\text{H}_{19}\text{F}_3\text{N}_3\text{O}$ [($\text{M}+\text{H}$) $^+$]: 374.1480; found: 374.1511, -5.91 ppm error.

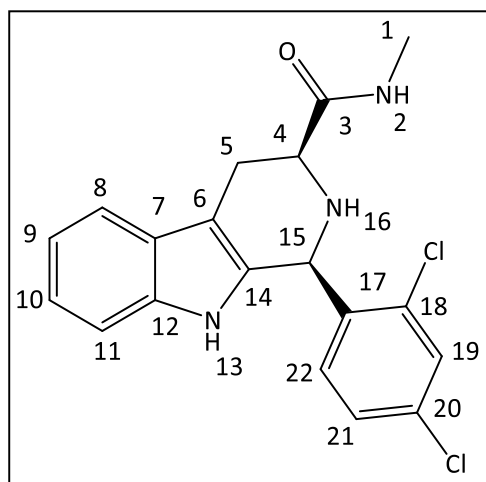
Preparation of (1S,3S)- 1-([3-trifluoromethyl]phenyl)-3-acetamide-1,2,3,4-tetrahydro- β -carboline 438:



According to **general procedure 13** L-Trp-NHMe **432** (1.2 g, 5.6 mmol, 1 equiv.), 3 Å molecular sieves (10 mg), 3-(trifluoromethyl)benzaldehyde **437** (1.07 g, 6.16 mmol, $p = 1.301\text{ g mL}^{-1}$, 820 μL , 1.1 equiv.) and trifluoroacetic acid (1.27 g, 11.2 mmol, $p = 1.478\text{ g mL}^{-1}$, 860 μL , 2 equiv.) were combined to afford white-off oil (99 mg, 0.26 mmol, 5%). **438**: $R_f = 0.39$ (9:1 dichloromethane/diethyl ether, det: KMnO_4); m.p. 188-190 °C; ^1H -NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 2.05$ (br.s, 1H, H_2), 2.82-2.83 (m, 3H, H_1), 2.87-2.91 (m,

^1H , H_{5a}), 3.32-3.39 (m, 1H, H_{5b}), 3.73 (dd, $J = 11.1, 4.3$ Hz, 1H, H_4), 5.23 (t, $J = 2.2$ Hz, 1H, H_{15}), 7.13-7.14 (m, 1H, H_9), 7.16-7.17 (m, 1H, H_{10}), 7.23 (d, $J = 2.0$ Hz, 1H, H_{11}), 7.48 (s, 1H, H_{18}), 7.49-7.51 (m, 1H, H_{23}), 7.54-7.57 (m, 1H, H_8), 7.62-7.64 (m, 2H, $\text{H}_{22}, \text{H}_{21}$), 7.66 (br.s, 1H, H_{13}); ^{13}C -NMR (75 MHz, CDCl_3 , 25 °C): $\delta = 25.6$ (C1), 26.0 (C5), 58.1 (C15), 110.5 (C6), 111.1 (C11), 118.5 (C8), 119.9 (C9), 122.4 (C10), 125.5 (q, $J = 3.8$ Hz) (C21, C22), 127.0 (C20), 129.6 (C18), 130.2 (C7), 131.6 (C14), 133.9 (C19), 136.3 (C12), 141.8 (C17), 173.1 (C3); IR (neat): ν_{max} (cm^{-1}) = 2990, 1652, 1531, 1443, 769, 701, 683; MS (ESI), 374 (MH^+), HRMS (ESI, m/z %) calcd. for $\text{C}_{20}\text{H}_{19}\text{F}_3\text{N}_3\text{O}$ [$(\text{M}+\text{H})^+$]: 374.1480; found: 374.1512, -7.27 ppm error.

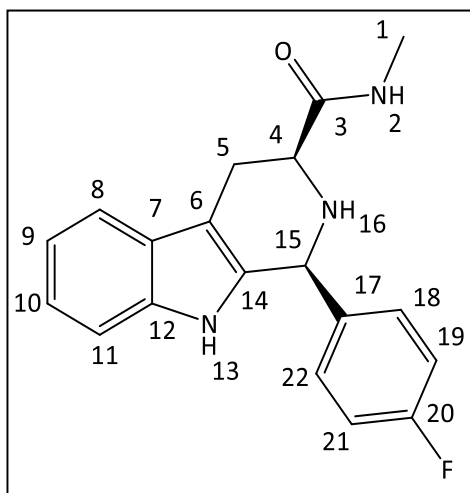
Preparation of (1S,3S)- 1-(2,4-dichlorophenyl)-3-acetamide-1,2,3,4-tetrahydro- β -carboline 440:



According to **general procedure 13** L-Trp-NHMe **432** (1.2 g, 5.6 mmol, 1 equiv.), 3 Å molecular sieves (10 mg), 2,4-dichlorobenzaldehyde **439** (1.07g, 6.16 mmol, 1.1 equiv.) and trifluoroacetic acid (1.27 g, 11.2 mmol, $p = 1.478$ g mL^{-1} , 860 μL , 2 equiv.) were combined to afford white solid (135 mg, 0.36

mmol, 6.75%). **440**: $R_f = 0.46$ (9:1 dichloromethane/diethyl ether, det: KMnO_4); m.p. 183-185 °C; $^1\text{H-NMR}$ (300 MHz, CDCl_3 , 25 °C): $\delta = 1.77$ (br.s, 1H, H_{16}), 2.80 (d, $J = 4.9$ Hz, 3H, H_1), 2.84 (dd, $J = 11.2, 2.5$ Hz, 1H, H_{5a}), 3.27-3.35 (m, 1H, H_{5b}), 3.68 (dd, $J = 11.1, 4.2$ Hz, 1H, H_4), 5.68 (br.s, 1H, H_{15}), 6.93 (d, $J = 4.9$ Hz, 1H, H_2), 7.10 (d, $J = 1.3$ Hz, 1H, H_8), 7.12-7.13 (m, 1H, H_{10}), 7.14 (d, $J = 1.3$ Hz, 1H, H_{21}), 7.16 (d, $J = 1.9$ Hz, 1H, H_{19}), 7.22 (s, 1H, H_{11}), 7.44-7.45 (m, 1H, H_{22}), 7.62 (d, $J = 6.8$ Hz, 1H, H_9), 7.95 (br.s, 1H, H_{13}); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3 , 25 °C): $\delta = 25.6$ (C1), 26.0 (C5), 54.7 (C15), 58.0 (C4), 110.6 (C6), 111.1 (C11), 118.4 (C9), 119.8 (C8), 122.3 (C10), 127.0 (C7), 127.9 (C19), 129.8 (C22), 130.7 (C21), 132.9 (C14), 134.8 (C20), 135.1 (C12), 136.3 (C18), 137.0 (C17), 173.1 (C3); IR (neat): ν_{max} (cm^{-1}) = 2985, 2967, 2911, 1661, 1617, 1584, 1464, 1182, 755; MS (ESI), 374 (MH^+), HRMS (ESI, m/z %) calcd. for $\text{C}_{19}\text{H}_{18}^{35}\text{Cl}_2\text{N}_3\text{O}$ [$(\text{M}+\text{H})^+$]: 374.0826; found: 374.0837, -0.5 ppm error.

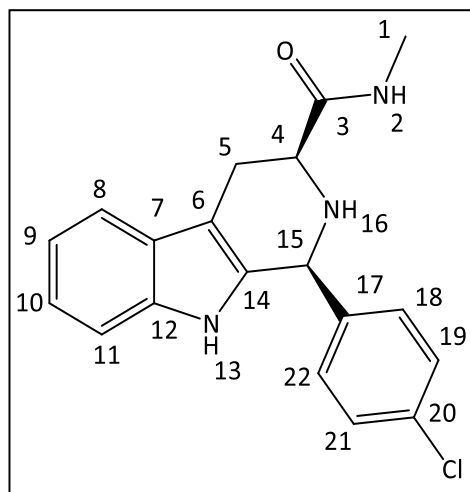
Preparation of (1S,3S)- 1-(4-fluorophenyl)-3-acetamide-1,2,3,4-tetrahydro- β -carboline 442:



According to **general procedure 13** L-Trp-NHMe **432** (500 mg, 2.3 mmol, 1 equiv.), 3 Å molecular sieves (10 mg), 4-fluorobenzaldehyde **441** (313 mg, 2.53 mmol, $p = 1.157 \text{ g mL}^{-1}$, 270 μL , 1.1 equiv.) and trifluoroacetic acid (524 mg, 4.6 mmol, $p = 1.478 \text{ g mL}^{-1}$, 350 μL , 2 equiv.) were combined to afford white solid (55 mg, 0.17 mmol, 7.43%). **442**: $R_f = 0.39$ (9:1 dichloromethane/diethyl ether, det: KMnO_4); m.p. 235-237 °C; $^1\text{H-NMR}$ (400 MHz, CD_3OD , 25 °C): $\delta = 2.79$ (s, 3H, H_1), 2.90-2.97 (m, 1H, H_{5a}), 3.19 (dt, $J = 13$, 2.3, 2.3, 2.3 Hz, 1H, H_{5b}), 3.80 (dd, $J = 11$, 4.2 Hz, 1H, H_4), 5.69 (s, 1H, H_{15}), 6.98-7.06 (m, 3H, H_9 , H_{10} , H_{19}), 7.18 (d, $J = 7.8$ Hz, 1H, H_{11}), 7.47 (d, $J = 7.3$ Hz, 1H, H_{18}), 7.66 (d, $J = 8.1$ Hz, 1H, H_{21}), 7.88 (d, $J = 7.8$ Hz, 1H, H_{22}), 8.06 (s, 1H, H_8); $^{13}\text{C-NMR}$ (100 MHz, CD_3OD , 25 °C): $\delta = 24.9$ (C1), 25.4 (C5), 53.4 (C15), 58.7 (C4), 108.7 (C6), 110.8 (C11), 117.4 (C18), 118.7 (C19), 121.3 (C9, C10), 122.4 (C8), 126.6 (C7), 129.0 (C21), 130.0 (C14), 132.1 (C22), 133.1 (C12), 137.1 (C20), 145.0 (C17), 174.6 (C3); IR (neat): ν_{max} (cm^{-1}) = 2985, 9850, 1650, 1586, 1473,

1280, 1118, 746, 696; MS (ESI), 324 (MH⁺), HRMS (ESI, m/z %) calcd. for C₁₉H₁₉FN₃O [(M+H)⁺]: 324.1512; found: 324.1540, -7.59 ppm error.

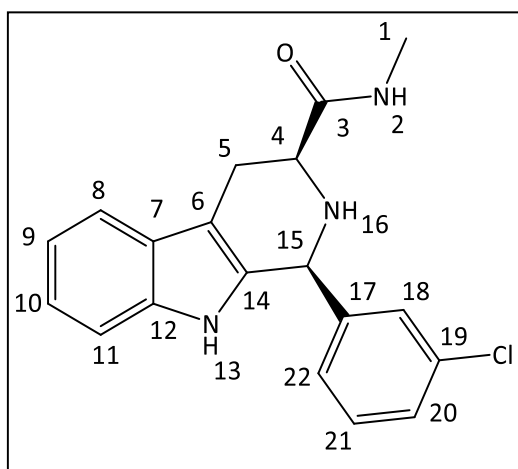
Preparation of (1S,3S)- 1-(4-chlorophenyl)-3-acetamide-1,2,3,4-tetrahydro-β-carboline 444:



According to **general procedure 13** L-Trp-NHMe **432** (500 mg, 2.3 mmol, 1 equiv.), 3 Å molecular sieves (10 mg), 4-chlorobenzaldehyde **443** (355 mg, 2.53 mmol, 1.1 equiv.) and trifluoroacetic acid (524 mg, 4.6 mmol, $p = 1.478$ g mL⁻¹, 250 μL, 2 equiv.) were combined to afford white solid (53 mg, 0.15 mmol, 6.8%). **444**: $R_f = 0.33$ (diethyl ether, det: KMnO₄); m.p. 177-178 °C; ¹H-NMR (400 MHz, CDCl₃, 25 °C): $\delta = 1.90$ (s, 1H, H₁₆), 2.82 (d, $J = 4.9$ Hz, 3H, H₁), 2.85-2.87 (m, 1H, H_{5a}), 3.33 (d, $J = 3.2$ Hz, 1H, H_{5b}), 3.70 (dd, $J = 11, 4.3$ Hz, 1H, H₄), 5.17 (s, 1H, H₁₅), 6.94 (d, $J = 4.2$ Hz, 1H, H₂), 7.11-7.17 (m, 2H, H₉, H₁₀), 7.25 (d, $J = 8.6$ Hz, 3H, H₁₁, H₁₉, H₂₁), 7.32-7.34 (m, 2H, H₁₈, H₂₂), 7.54 (d, $J = 7.3$ Hz, 1H, H₈), 7.68 (s, 1H, H₁₃); ¹³C-NMR (100 MHz, CDCl₃, 25 °C): $\delta = 23.7$ (C₁), 24.1 (C₅), 56.3 (C₄), 56.5 (C₁₅), 108.5 (C₆), 109.2 (C₁₁), 116.6 (C₈), 118.0 (C₁₀), 120.4 (C₉), 125.3 (C₇), 127.4 (C₁₉, C₂₁), 128.1 (C₁₈, C₂₂), 132.0 (C₁₂), 132.7

(C14), 134.5 (C20), 137.4 (C17), 171.2 (C3); IR (neat): ν_{\max} (cm^{-1}) = 3002, 2950, 1644, 1540, 1489, 1140, 1066, 794, 741; MS (ESI), 340 (MH^+), HRMS (ESI, m/z %) calcd. for $\text{C}_{19}\text{H}_{19}^{35}\text{ClN}_3\text{O}$ $[(\text{M}+\text{H})^+]$: 340.1216; found: 340.1243, -6.25 ppm error.

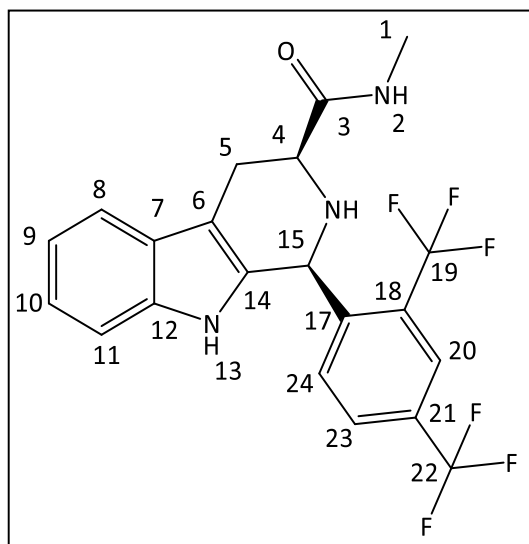
Preparation of (1S,3S)- 1-(3-chlorophenyl)-3-acetamide-1,2,3,4-tetrahydro- β -carboline 446:



According to **general procedure 13** L-Trp-NHMe **432** (500 mg, 2.3 mmol, 1 equiv.), 3 Å molecular sieves (10 mg), 3-chlorobenzaldehyde **445** (355 mg, 2.53 mmol, $p = 1.241$ g mL^{-1} , 290 μL , 1.1 equiv.) and trifluoroacetic acid (524 mg, 4.6 mmol, $p = 1.478$ g mL^{-1} , 350 μL , 2 equiv.) were combined to afford white solid (104 mg, 0.33 mmol, 13%). **446**: $R_f = 0.45$ (diethyl ether, det: KMnO_4); m.p. 196-198 °C; $^1\text{H-NMR}$ (400 MHz, CDCl_3 , 25 °C): $\delta = 1.85$ (s, 1H, H_{16}), 2.85 (d, $J = 4.5$ Hz, 3H, H_1), 2.88-2.90 (m, 1H, H_{5a}), 3.39 (dd, $J = 15.7, 4.2$ Hz, 1H, H_{5b}), 3.76 (dd, $J = 11.1, 4.3$ Hz, 1H, H_4), 5.20 (s, 1H, H_{15}), 6.93 (d, $J = 4.2$ Hz, 1H, H_2), 7.12-7.18 (m, 2H, $\text{H}_9, \text{H}_{10}$), 7.22-7.24 (m, 2H, $\text{H}_{20}, \text{H}_{21}$), 7.31-7.35 (m, 3H, $\text{H}_{18}, \text{H}_{22}, \text{H}_{11}$), 7.52 (s, 1H, H_{13}), 7.57 (d, $J = 7.6$ Hz, 1H, H_8); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 25 °C): $\delta = 25.6$ (C1), 25.9 (C5), 58.2 (C4), 58.6 (C15), 110.6 (C6),

111.0 (C20), 118.6 (C8), 119.9 (C9), 122.4 (C10), 126.6 (C21), 127.1 (C7), 128.7 (C22), 129.0 (C11), 130.4 (C18), 133.5 (C14), 135.1 (C19), 136.3 (C12), 142.8 (C8), 173.0 (C3); IR (neat): ν_{\max} (cm⁻¹) = 3545, 3050, 2988, 1666, 1592, 1570, 1518, 1263, 1138, 1077, 60, 746, 696; MS (ESI), 340 (MH⁺), HRMS (ESI, m/z %) calcd. for C₁₉H₁₉³⁵ClN₃O [(M+H)⁺]: 340.1216; found: 340.1243, -6.25 ppm error.

Preparation of (1S,3S)- 1-([2,4-bis(trifluoromethyl)phenyl]-3-acetamide-1,2,3,4-tetrahydro- β -carboline **448:**

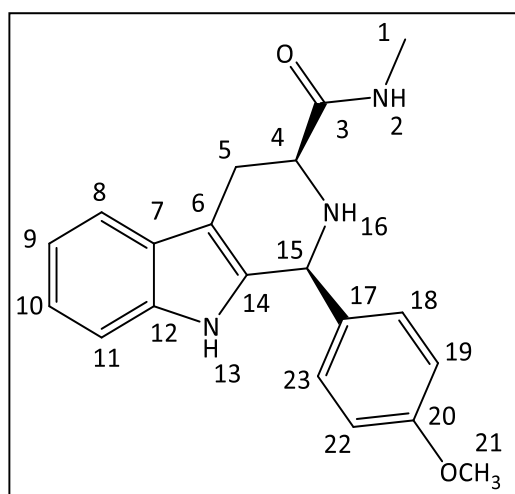


According to **general procedure 13** L-Trp-NHMe **432** (300 mg, 1.38 mmol, 1 equiv.), 3 Å molecular sieves (10 mg), 2,4-bis(trifluoromethyl)benzaldehyde **447** (417 mg, 1.72 mmol, ρ = 1.470 g mL⁻¹, 280 μ L, 1.25 equiv.) and trifluoroacetic acid (314 mg, 2.76 mmol, ρ = 1.478 g mL⁻¹, 210 μ L, 2 equiv.) were combined to afford white solid (33 mg, 0.07 mmol, 5.5%). **448**: R_f = 0.36 (diethyl ether, det: KMnO₄); m.p. 215-217 °C; ¹H-NMR (300 MHz, CDCl₃, 25 °C): δ = 1.65 (br.s, 1H, H₁₆), 2.86 (d, J = 4.9 Hz, 3H, H₁), 2.90 (s, 1H, H_{5a}), 3.40 (d, J = 15.7 Hz, 1H, H_{5b}), 3.77 (dd, J = 11.1, 4.3 Hz, 1H, H₄), 5.22 (s, 1H, H₁₅), 6.95 (s, 1H, H₂), 7.08 (t, J = 8.4 Hz, 2H, H₉, H₁₀), 7.16 (t, J = 7.7 Hz, 2H, H₂₀, H₂₃), 7.30-7.33

(m, 1H, H₁₁, H₈), 7.45 (s, 1H, H₁₃), 7.57 (d, *J* = 7.6 Hz, 1H, H₂₄); ¹³C-NMR (75 MHz, CDCl₃, 25 °C): δ = 25.6 (C1), 25.9 (C5), 58.2 (C4), 58.4 (C15), 110.5 (C11), 111.9 (C11), 115.9 (C10), 116.2 (C9), 118.5 (C24), 119.9 (C20), 122.3 (C23), 126.4 (C7), 1327.2 (C14), 130.2 (C8), 130.3 (C21), 134.0 (C12), 136.2 (C18), 136.5 (C17), 173.1 (C3); IR (neat): ν_{max} (cm⁻¹) = 3010, 2943, 1652, 1604, 1508, 1459, 1163, 763, 750, 691; MS (ESI), 442 (MH⁺), HRMS (ESI, *m/z* %) calcd. for C₂₁H₁₈F₆N₃O [(M+H)⁺]: 442.1354; found: 442.1388, -7.61 ppm error.

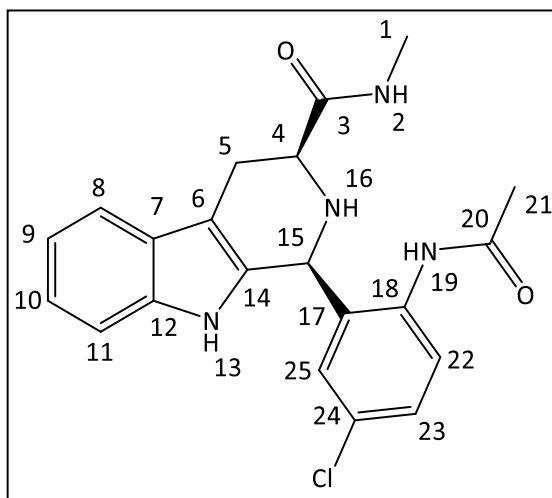
Preparation of (1*S*,3*S*)- 1-([4-methoxyphenyl]-3-acetamide-1,2,3,4-

tetrahydro-β-carboline **450**:



According to **general procedure 13** L-Trp-NHMe **432** (200 mg, 0.9 mmol, 1 equiv.), 3 Å molecular sieves (10 mg), 4-methoxybenzaldehyde **449** (134 mg, 0.99 mmol, *p* = 1.119 g mL⁻¹, 120 μL, 1.25 equiv.) and trifluoroacetic acid (205 mg, 1.8 mmol, *p* = 1.478 g mL⁻¹, 140 μL, 2 equiv.) were combined to afford the crude as yellow oil. No characterisation of **450** was attempted.

Preparation of (1S,3S)- 1-([2-acetamino-5-chlorophenyl]-3-acetamide-1,2,3,4-tetrahydro- β -carboline **453:**



According to **general procedure 13** L-Trp-NHMe **432** (200 mg, 0.9 mmol, 1 equiv.), 3 Å molecular sieves (10 mg), 2-acetamino-5-chlorobenzaldehyde **452** (200 mg, 1.0 mmol, 1.1 equiv.) and trifluoroacetic acid (205 mg, 1.8 mmol, $p = 1.478 \text{ g mL}^{-1}$, 140 μL , 2 equiv.) were combined to afford the crude as yellow oil. No characterisation of **453** was attempted.

8 References:

- 1- (a) L. F. Tietze, U. Beifuss, *Angew. Chemie. Int. Ed.*, **1993**, 32, 131. (b) L. F. Tietze. *Chem. Rev.*, **1996**, 96, 115.
- 2- B. M. Trost, *Science*, **1991**, 254, 1471.
- 3- R. Robinson, *J. Chem. Soc. Trans.*, **1917**, 111, 762-768.
- 4- U. K. Bhadriah, S. Kehavamuthy, M. Madegowda, S. D. Doddaramappa, S. Ningaiah, *Synth. Commun.*, **2014**, 2222-2231.
- 5- K. A. Scheidt, B.E. Maki, A. Chan, E.M. Phillips, *Org. Lett.*, **2007**, 9 (2), 371-374.
- 6- M. X. Liu, J. R. Li, K. Zheng, H. Yao, Q. Zhang, D.X. Shi, *Tetrahedron Lett.*, **2015**, 71 (40), 7658-7662.
- 7- (a) A. Kumar, P. Kaswan, K. Pericherla, D. Purohit, *Tetrahedron Lett.*, **2015**, 56 (3), 549-553. (b) A. Balanta, C. Godard, C. Claver, *Chem. Soc. Rev.*, **2011**, 40 (10), 4973-4985; G.P. McGlacken and I.J. Fairlamb, *Eur. J. Org. Chem.*, **2009**, 2009 (24), 4011-4029.
- 8- M. Hussain, D. T. Thanh Tùng, P. Langer, *SYNLETT*, **2009**, 11, 1822-1826.
- 9- K.C. Nicolaou, D. J. Edmonds, P.G. Bulger, *Angew. Chemie. Int. Ed.* **2006**, 45 (43), 7134-7186.
- 10- H. Pellissier, *Tetrahedron Lett.*, **2006**, 62 (8), 1619-1665.
- 11- L.E. Overman, C.M. Gasparski, P.M. Herrinton, J.P. Wolfe, *Tetrahedron Lett.*, **2000**, 41 (49), 9431-9435.
- 12- (a) H. Pellissier, *Tetrahedron*, **2006**, 62 (10), 2143-2173, (b) S. V. Ley, D. S. Brown, J. A. Clase, A. J. Fairbanks, I. C. Lennon, H. M. I. Osborn, E. S. E. Stokes

- (nQe Owen), D. J. Wadsworth, *J. Chem. Soc. Perkin Trans. 1*, **1998**, 0, 2259-2276.
- 13- L. E. Overman and M.A. Kakimoto, *J. Am. Chem. Soc.*, **1979**, 101 (5), 1310-1312.
- 14- S. Han and S. Jeon, *J. Am. Chem. Soc.*, **2017**, 139 (18), 6302-6305.
- 15- M. D. Shair, C. Chen, M. E. Layton, S. M. Sheehan, *J. Am. Chem. Soc.*, **2000**, 122 (30), 7424-7425
- 16- R. A. Gibbs and W. H. Okamura, *J. Am. Chem. Soc.*, **1988**, 110 (12), 4062-4063.
- 17- R. J. K. Taylor, and X. D. Wei, *Tetrahedron Lett.*, **1998**, 39, 3815.
- 18- R. E. Ireland, and D. W. Norbeck, *J. Org. Chem.*, **1985**, 50, 2198.
- 19- A. G. Barrett, O. Hamprecht, M. Ohkuho, *J. Org. Chem.*, **1997**, 62, 9376-9378.
- 20- M. M. Mojtahedi, M. S. Abaee, A. J. Arabzadeh, *J. Org. Chem.*, **2014**, 3 (1), 11-16.
- 21- R. J. K. Taylor, and L. Blackburn, *Org. Lett.*, **2001**, 3 (11), 1637-1639.
- 22- R. J. Taylor, M. F. Oswald, S. A. Raw, *Chem. Communi.*, **2005**, 17, 2253-2255.
- 23- S. L. Suib, S. Biswas, K. Mullick, S. Y. Chen, A. Gudz, D. M. Carr, C. Mendoza, A. M. Angeles-Boza, *Applied Catalysis B: Environmental*. **2017**, 203, 607-614.
- 24- J. D. Waetzig and P. R. Hanson, *Chemtracts*, **2007**, 19, 157-167.
- 25- G. Wittig and G. Geissler, *Liebigs. Ann. Chem.*, **1953**, 580, 44.
- 26- D. J. Peterson, *J. Org. Chem.*, **1968**, 33, 780-784.
- 27- M. Julia and J. M. Paris, *Tetrahedron Lett.*, **1973**, 14 (49), 4833-4836.
- 28- J. Baudin, G. Harean, S. Julia, *Tetrahedron Lett.* **1991**, 32, 1175-1178.
- 29- G. Wittig and G. Geissler, *Eur. J. Org. Chem.*, **1953**, 580 (1), 44-57.
- 30- A. W. Johnson, *Ylide Chemistry*, Academic press, New York, **1966**.
- 31- M. Trost, and L. S. Melvin, *Sulfur Ylide*, Academic press, New York, **1975**.

- 32- H. Staudinger, and J. Meyer, *Helv. Chim. Acta.*, **1919**, 2 (1), 635-646.
- 33- (a) H. Pommer, and P. C. Thieme, *Top. Cure Chem.*, **1983**, 109, 165-188; (b) U. Pindur, R. Adam, *Helv. Chim. Acta*, **1990**, 73, 827-838.
- 34- (a) S. Trippett, and S. T. Ross, *J. Org. Chem.* **1962**, 27 (3), 998-1000, (b) H. J. Bestmann, *Angew. Chim.* **1977**, 89 (6), 361-376. (c) Z. Z. Huang, X. C. Yu, X. Huang, *Tetrahedron Lett.* **2002**, 43 (38), 6823-6825; Z. Z. Huang, X. C. Yu, X. Huang, *J. Org. Chem.* **2002**, 67 (23), 8261-8264.
- 35- M. Schlosser, R. Oi, B. Schaub, *Phosphorus Sulfur*, **1983**, 18, 71.
- 36- B. E. Maryanoff, A. B. Aetiz, *Phosphorus Sulfur*, **1986**, 27, 167.
- 37- O. I. kolodiaznyi, *Phosphorus Ylides*, Wily- VCH, Weinheim, **1999**.
- 38- E. Vedejs, K. A. J. Snoble, *J. Am. Chem. Soc.* **1973**, 95 (17), 5778-5780.
- 39- R. A. Neumann, S. Berger, *Eur. J. Org. Chem.* **1998**, 1998 (6), 1085-1087.
- 40- J. Clayden, N. Greeves, S. Warren, *Organic Chemistry*, second edition, **2012**, 691-693.
- 41- E. Vedejs, M. J. Peterson, *Top. Stereochem.* **1994**, 21, 1-157.
- 42- H. J. Bestmann, K. Roth, E. Wilhelm, R. Bohme, H. Burzlaff, *Angew. Chem. Int. Ed.* **1979**, 18 (11), 876-877.
- 43- E. Vedejs, C. F. Marth, *J. Am. Chem. Soc.* **1989**, 111 (4), 1519-1520.
- 44- R. J. K. Taylor, E. Roman, M. Reid, E. Q. Steven, *Tetrahedron*, **2006**, 62 (28), 6673-6680.
- 45- S. Xu, S. Zhu, J. Shang, J. Zhang, Y. Tang, J. Dou, *J. Org. Chem.*, **2014**, 79 (8), 3696-3703.
- 46- M. A. Sultan, H. Al-Shamari, H. Abdelall, A. I. Almansour, U. Karama. *J. Chem. Soc. Pak.*, **2017**, 39 (1), 92-96

- 47- J. Lu and P. H. Toy. *Chem. Asian J.*, **2011**, 6 (9), 2251-2254.
- 48- B. Schmidt & M. Riemer. *Synthesis*, **2016**, 48 (01), 141-149.
- 49- J. McNulty, P. Das, *Tetrahedron Lett.*, **2009**, 50 (41), 5737-5740.
- 50- J. Clayden, N. Greeves, S. Warren, *Organic Chemistry*, second edition, **2012**, 922.
- 51- R. B. Woodward, R. Hoffmann, *Angew. Chemie. Int Edn. Engl.*, **1969**, 8 (11), 781-853.
- 52- (a) I. N. Nazarov and I. I. Zaretskaya, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, **1941**, 211-224. (b) J. Motoyoshiya, T. Yazaki, S. Hayashi. *J. Org. Chem.* **1991**, 56 (2), 735-740.
- 53- (a) E. A. Braude and J. A. Coles, *J. Chem. Soc.* **1952**, 0, 1430-1433; (b) L. A. Paquette, W. E. Fristad, D. S. Dime, T. R. Bailey. *J. Org. Chem.* **1980**, 45 (15), 3017-3028; S. Hirano, T. Hiyama, H. Nozaki. *Tetrahedron Lett.* **1974**, 15, 1429-1430; (c) C. J. Rieder, K.J. Winberg, F.G. West. *J. Am. Chem. Soc.*, **2009**, 131 (22), 7504-7505.
- 54- W. He, X. Sun, and A.J. Frontier. *J. Am. Chem. Soc.*, **2003**, 125 (47), 14278-14279.
- 55- (a) S. Ranganathan, *Resonance: Journal of Science Education*, **2011**, 16 (12), 1211-1222. (b) J. Clayden, N. Greeves, S. Warren. *Organic Chemistry*, second edition, **2012**, 879-892.
- 56- J. D. Winkler, *Chem. Rev.*, **1996**, 96 (1), 167-176.
- 57- I. E. Marko, P. Seres, T. M. Swarbrick, I. Sataton, H. Adams, *Tetrahedron Lett.*, **1992**, 33 (38), 5649-5652.

- 58- I. E. Marko, T. M. Swarbrick, L. Kennard, *Tetrahedron Lett.*, **1991**, 32 (32), 2549-
2552.
- 59- R. J. K. Taylor, and S. Raw, *J. Am. Chem. Soc.*, **2004**, 126 (39), 12260-12261.
- 60- R. J. K. Taylor, S. Raw, *Chem. Commun.*, **2004**, 0, 508-509.
- 61- D.S. Seigler, Plant secondary metabolism. Springer Science & Business Media,
2012.
- 62- W. A. Creasy, *The monoterpenoid Indole Alkaloids. In Heterocyclic Compounds, Indole Series*; J. E. Saxton., Ed.; John Wiley and Sons: New York, **1983**.
- 63- J.R. Hanson, *The chemistry of fungi*, Cambridge: RSC, **2008**, 173.
- 64- M. Lounasmaa, P. Hanhinen, M. Westersund. *In the Alkaloids, Chemistry and Biology*, **1999**, 52, 103-195.
- 65- L.K. Hamaker and J.M. Cook. The synthesis of macroline related sarpagine alkaloids (Vol. 9, p. 23). Elsevier Science: New York. **1995**.
- 66- A. Chatterjee, J. Banerji, A. Banerji. *J. Ind. Chem. Soc.*, **1974**, 5, 156-170.
- 67- C. W. Wright, D. Allen, Y. Cai, J. D. Phillipson, I. M. Said, G. C. Kirby, D. C. Warhurst. *Phytotherapy Research*, **1992**, 6 (3), 121-124.
- 68- N. Keawpradub, G.C. Kirby, J.C.P. Steele and P.J. Houghton. *Planta medica*, **1999**, 65 (8), 690-694.
- 69- W. Peczynska-Czoch, F. Pognan, L. Kaczmarek, J. Boratynski. *J. med. chem.*, **1994**, 37(21), 3503-3510.
- 70- J. Winters, and N. Di Mola. West German Patent 2442513. *In Chem. Abstr*, **1975** (Vol. 82, p. 156255).
- 71- C. Moquin, and M. Guyot. *Tetrahedron Lett.*, 1984, 25 (44), 5047-5048; C. Moquin-Patthey, and M. Guyot. *Tetrahedron*, **1989**, 45 (11), 3445-3450; T. Oda,

- J.S. Lee, Y. Sato, Y. Kabe, S. Sakamoto, H. Handa, R. E. P. Mangindaan, M. Namikoshi. *Marine Drugs*, **2009**, 7 (4), 589-599.
- 72- R. Ikeda, T. Kimura, T. Tsutsumi, S. Tamura, N. Sakai, T. Konakahara, *Bioorg. Med. Chem. Lett.*, **2012**, 22 (10), 3506-3515.
- 73- K. P. Lippke, W. G. Schunack, W. Wenning, W. E. Mueller, *J. Med. Chem.*, **1983**, 26 (4), 499-503; A. K. Saxena, P. C. Jain, N. Anand, P. R. Dua, *J. Med. Chem.*, **1973**, 16 (5), 560-564; G. Haffer, K. Nickisch, U. Tilstam. *Heterocycles*, **1998**, 48 (5), 993-998.
- 74- F. Bracher and D. Hildebrand. *Eur. J. Org. Chem.*, **1992**, 1992 (12), 1315-1319.
- 75- (a) K.M. Brummond, J.R. Goodell, M.G. LaPorte, L. Wang, X.Q. Xie. *Beilstein J. Org. Chem.*, **2012**, 8, 1048; (b) D. Blanco-Ania, P.H. Hermkens, L.A. Sliedregt, H.W. Scheeren, F.P. Rutjes. *J. Comb. Chem*, **2009**, 11 (4), 539-546; (c) A. Spindler, K. Stefan, and M. Wiese. *J. Med Chem.*, **2016**, 59 (13), 6121-6135; (d) T. Herraiz. *J. Agric. food Chem.*, **2000**, 48 (10), 4900-4904; (e) R.N. Rao, B. Maiti and K. Chanda. *ACS Comb. Sci.*, **2017**, 19 (4), 199-228; (f) L. A.Doyle, W. Yang, L. V. Abruzzo, T. Krogmann, Y. Gao, A. K. Rishi, D. D. Ross. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, 95 (26), 15665-15670.
- 76- T.P. Singh and O.M. Singh. *J. Chem. Sci.*, **2016**, 128 (4), 565-572.
- 77- (a) Y. Yang, L. Li, Y. He, J. Luo, Y. Liang, *Tetrahedron*, **2014**, 70 (3), 702-707. (b) A. L. Pumphrey, H. Dong, T. G. Driver, *Angew. Chemie., Int. Ed.* **2012**, 51 (24), 5920-5923; (c) H. Shang, Y.Tian, J. Luo, L. Li, Y. Tang, Z. Zou, *RSC Adv.* **2016**, 6 (37), 30835-30839; (d) H. Song, Y. Liu, Q. Wang, *Org. Lett.* **2013**, 15 (13), 3274-3277.

- 78- (a) F. Liu, and Q.D. You. *Synth. Communi.*, **2007**, 37 (22), 3933-3938; (b) P. Campiglia, I. Gomez-Monterrey, T. Lama, E. Novellino and P. Grieco. *Molecular diversity*, **2004**, 8 (4), 427-430.
- 79- S.G. Wang, Z.L. Xia, R.Q. Xu, X.J. Liu, C. Zheng, S.L. You. *Angew. Chemie. Int. Ed.*, **2017**, 129 (26), 7548-7551.
- 80- (a) E.J. Cochrane, L.A. Hassall, I. Coldham. *J. Org. Chem.*, **2015**, 80 (11), 5964-5969; (b) M. Sayyad, I.A. Wani, R. Babu, Y. Nanaji. *J. Org. Chem.*, **2017**, 82(5), 2364-2374.
- 81- (a) C. Y. Wu and C. M. Sun. *Synlett*, **2002**, 10, 1709-1711; (b) P. Bikash, J. Parasuraman, S. Venkatachalam. *Synth. Commun.* **2003**, 33 (13), 2339-2348.
- 82- H. Song, Y. Liu, Q. Wang. *Org. Lett.*, **2013**, 15 (13), 3274-3277.
- 83- W. Gul, M.T. Hamann. *Life Sci.*, **2005**, 78 (5), 442-453.
- 84- R. Cao, W. Peng, Z. Wang, A. Xu. *Curr. Med. Chem.* **2007**, 14 (4), 479-500.
- 85- (a) K.L. Rinehart, J. Kobayashi, G.C. Harbour, R.G. Hughes, S.A. Mizesak, T.A. Scahill. *J. Am. Chem. Soc.* **1984**, 106 (5), 1524-1526; (b) K.L. Rinehart, J. Kobayashi, G.C. Harbour, J. Gilmore, M. Mascal, T.G. Holt, L.S. Shield, F. Lafargue. *Am. Chem. Soc.* **1987**, 109 (11), 3378-3387.
- 86- J.H. Van Maarseveen, P.H.H. Hermkens, E. de Clercq, J. Balzarini, H.W. Scheeren, C.G. Kruse. *J. Med. Chem.* **1992**, 35 (17), 3223-3230.
- 87- J. F. Mille, E. M. Turner, R. G. Sherrill, K. Gudmundsson, A. Spaltenstein, P. Sethna, K.W. Brown, R. Harvey, K.R. Romines, P. Golden. *Bioorg. Med. Chem. Lett.* **2010**, 20 (1), 256-259.
- 88- A. Daugan, P. Grondin, C. Ruault, D.G. le Monnier, H. Coste, J. Kirilovsky, F. Hyafil, R. Labaudiniere. *J. Med. Chem.* **2003**, 46 (21), 4525-4532.

- 89- Y. Shen, Y. Chang, C. Lin, C. Liaw, Y.H. Kuo, L. Tu, S.F. Yeh, *J. Chern. Mar. Drugs* **2011**, 9 (2), 256-277.
- 90- R. Skouta, M. Hayano, K. Shimada, B.R. Stockwell. *Bioorg. Med. Chem. Lett.* **2012**, 22 (17), 5707-5713.
- 91- S. Hotha, J. C. Yarrow, J. G. Yang, S. Garrett, K. V. Renduchintala, T. U. Mayer, T. M. Kapoor. *Angew. Chemie.*, **2003**, 115 (21), 2481-2484.
- 92- P. Serafini, K. Meckel, M. Kelso, K. Noonan, J. Califano, W. Koch, L. Dolcetti, V. Bronte, I. J. *Exp. Med.* **2006**, 203 (12), 2691-2702.
- 93- R.A. Davis, S. Duffy, V.M. Avery, D. Camp, J.N.A. Hooper, R.J. Quinn. *Tetrahedron Lett.* **2010**, 51 (4), 583-585.
- 94- S.T.S. Chan, A.N. Pearce, M.J. Page, M. Kaiser, B.R. Copp. *J. Nat. Prod.* **2011**, 74 (9), 1972-1979.
- 95- A. Gellis, A. Dumètre, G. Lanzada, S. Hutter, E. Ollivier, P. Vanelle, N. Azas. *Pharmacother.* **2012**, 66 (5), 339-347.
- 96- L. Gupta, K. Srivastava, S. Singh, S.K. Puri, P.M.S. Chauhan. *Bioorg. Med. Chem. Lett.* **2008**, 18 (11), 3306-3309.
- 97- M. Rottmann, C. McNamara, B.K.S. Yeung, M.C.S. Lee, B. Zou, B. Russell, P. Seitz, D.M. Plouffe, N.V. Dharia. *J. Tan. Science*, **2010**, 329 (5996), 1175-1180.
- 98- B.K.S. Yeung, B. Zou, M. Rottmann, S.B. Lakshminarayana, S.H. Ang, S.Y. Leong, J. Tan, J. Wong, S. Keller-Maerki, C. Fischli. *J. Med. Chem.* **2010**, 53 (14), 5155-5164.
- 99- World Malaria Report **2012**. Available online: http://www.who.int/malaria/publications/world_malaria_report_2012/report/en/index.html (accessed on 21 Sep 2017).

- 100- IFPMA Developing World Health Partnerships: Novartis R&D for Malaria. **2006**. Available online: <http://partnerships.ifpma.org/partnership/novartis-r-d-for-malaria> (Accessed on 23 Sep 2017).
- 101- J. Clayden, N. Greeves, S. Warren, Organic Chemistry, second edition, **2012**, 924.
- 102- A. Mesmaeker, E. Percheron, S. Catak, D. Zurwerra, R. Staigar, M. Lachia, *Tetrahedron Lett.*, **2014**, 55 (15), 2446-2449.
- 103- C. Saa, L. Castedo, C. Rodriguez, S. Rubin, J. Varela, *J. Am. Chem. Soc.* **2006**, 128 (29), 9262-9263.
- 104- R. Liu, J. Lian, S. Pal, H. Shen, *J. Am. Chem. Soc.*, **2003**, 125 (51), 15762-15763.
- 105- T. Akiyama, k. Fuchibe, k. Sangue, *Org. Lett.*, **2004**, 6 (3), 353-355.
- 106- J. Ellman, R. Bergman, S. Yotphan, *J. Am. Chem. Soc.*, **2008**, 130 (8), 2452-2453.
- 107- E. Marvell, C. Hitton, M. Cleary, *J. Org. Chem.* **1983**, 48 (23), 4272-4275.
- 108- T. Miyashi, Y. Takahashi, Y. Ohya , H. Ikeda, *J. Chem. Soc. Chem. Commun.*, **1995**, 0, 1749-1750.
- 109- A. de Meijere, K. Voigt, P. Zezhwitz, K. Rosaur, A. Iansky, A. Adams, O. Reiser, *Eur. J. Org. Chem.*, **1998**, 1998 (8), 1521-1534.
- 110- A. Fallis, M. Clay, N. Nguyen, P. Tessier, *Org. Lett.*, **2005**, 7 (5), 767-770.
- 111- S. Tilve, P. Torney, R. Shirsat, *Synlett*, **2014**, 25 (15), 2121-2126.
- 112- Y. Tang, B. Zhu, Q. Shen, Z. Xie, P. Cao, X. Sun, *Org. Lett.*, **2009**, 11 (14), 3048-3051.
- 113- (a) Q. Zhou, W. Li, J. Xie, M. Yuan, *Green Chem.*, **2014**, 16, 4081-4085; (b) C. Battilocchio, J. M. Hawkins, S. V. Ley, *Org. Lett.*, **2013**, 15(9), 2278-2281.

- 114- W.J. Bailey, E.J. Fetter, J. Economy, *J. Org. Chem.*, **1962**, 27 (10), 3479-3482.
- 115- R. W. Lenz, *Macromolecular*, **1969**, 2 (2), 129-135.
- 116- M. Sechi, M. Derudas, R. Dallochio, A. Dessi, A. Bacchi, L. Sannia, F. Carta, M. Palomba, O. Ragab, C. Chan, R. Shoemaker, S. Sei, R. Dayam, N. Neamati, *J. Med. Chem.*, **2004**, 47 (21), 5298-5310.
- 117- U. Atsushi, T. Masanori, W. N. O. Wylie, N. Masayoshi, I. Takao, H. Zhaomin, *Chem. Asian J.*, **2015**, 10(4), 1010-1016
- 118- J. Clayden, N. Greeves, S. Warren, Organic Chemistry, second edition, **2012**, 1170.
- 119- (a) C.E. Murar, F. Thuaud, J.W. Bode. *J. Am. Chem. Soc.*, **2014**, 136 (52), 18140-18148; (b) G. Primault, J.Y. Legros, J.C. Fiaud. *J. org. Chem.*, **2003**, 687 (2), 353-364.
- 120- (a) E. B. Skibo and C. Xing, *J. Med. Chem.* 2001, 44 (22), 3545-3562; (b) E. B. Skibo, C. Xing, T. Groy, *Bioorg. Med. Chem.* **2001**, 9 (9), 2445-2459.
- 121- J.D. Freed, D. J. Hart, N.A. Magomedov, *J. Org. Chem.*, **2001**, 66 (3), 839-852.
- 122- A. Karadeolian and M.A. Kerr, *Angew. Chemie. Int. Ed.*, **2010**, 49 (6), 1133-1135.
- 123- H. J. Dilek, K. Dogutan, M. Ptasze, k. S. Lindsey, *Tetrahedron*, **2007**, 63 (1), 37-55.
- 124- (a) N. Krogsgaard-Larsen, M. Begtrup, K. Frydenvang, J. Kehler. *Tetrahedron*, **2010**, 66 (47), 9297-9303; (b) K. Ohsawa, M. Yoshida, T. Doi, *J. Org. Chem.*, **2013**, 78 (7), 3438-3444.
- 125- O. Kundrat, H. Dvorakova, V. Eigner, P. Lhotak, *J. Org. Chem.*, **2010**, 75 (2), 407-411.

- 126- D. Evans, S. Kaldor, T. Jones, J. Clardy, T. Stout, *J. Am. Chem. Soc.*, **1990**, 112 (19), 7001-7031.
- 127- J. Mao, F. Liu, M. Wang, L. Wu, B. Zhen, S. Liu, J. Zhong, Q. Bian, P. J. Walsh, *J. Am. Chem. Soc.*, **2014**, 136 (50), 17662-17668.
- 128- L. L. Anderson W. H. Pecak, J. Son, A. J. Burnstine, *Org. Lett.*, **2014**, 16 (13), 3440-3443.
- 129- G. Michaelis, and H. V. Gimborn, *Chem. Ber.* **1894**, 27 (1), 272-277.
- 130- X. M. Zhang, and F. G. Bordwell, *J. Am. Chem. Soc.* **1994**, 116 (3), 968-972.
- 131- H. Ming-Jie, X. De-Cai, Y. Xin-Shan, *Chem. Commun.*, **2012**, 48, 11079-11081.
- 132- R. W. Lang, H. J. Hansen, *Org. Syn. Coll.*, **1990**, 7, 232 (Org. Syn., 1984, 62, 202-205).
- 133- J. Vicente, M. T. Chicote, M. C. Lagunas, P. G. Jones, *J. Chem. Soc., Dalton Trans.* **1991**, 2579-2583.
- 134- A. J. Wangelin, R. Fichtler, J. Neudorfl, *Org. Biomol. Chem.*, **2011**, 9, 7224-7236.
- 135- J. K. Laha and N. Dayal, *Org. Lett.*, **2015**, 17 (19), 4742-4745.
- 136- D. J. Kerr, C. Metje, B. L. Flynn, *Chem. Commun.*, **2003**, 0, 1380-1381.
- 137- W. He, X. F. Sun, A. J. Frontier, *J. Am. Chem. Soc.*, **2003**, 125 (47), 14278-14279.
- 138- C. Bee, E. Leclerc, M. A. Tius, *Org. Lett.*, **2003**, 5 (26), 4927-4930.
- 139- M. Janka, W. He, A. J. Frontier, R. Eisenberg, *J. Am. Chem. Soc.*, **2004**, 126 (22), 6864-6865.

- 140- (a) D. A. Klumpp, Y. Zhang, M. J. O'Connor, P. M. Esteves, L. S. DeAlmeida, *Org. Lett.* **2007**, 9, 3085-3088; (b) R. Singh, M. K. Parai, G. Panda, *Org. Biomol. Chem.* **2009**, 7, 1858-1867.
- 141- (a) M. Amere, J. Blanchet, M. C. Lasne, J. Rouden, *Tetrahedron Lett.* **2008**, 49, 2541-2545; (b) D. R. Williams, L. A. Robinson, C. R. Nevill, J. P. Reddy, *Angew. Chemie. Int. Ed.*, **2007**, 46 (6), 915-918.
- 142- P. Bachu and T. Akiyama, *Bioorg. & Med. Chem. Lett.*, **2009**, 19 (14), 3764-3766.
- 143- W. He, I. R. Herrick, T. A. Atesin, P. A. Caruana, C. A. Kellenberger, A. J. Frontier, *J. Am. Chem. Soc.*, **2008**, 130 (3), 1003-1011.
- 144- M. Janka, W. He, A. J. Frontier, R. Eisenberg, *J. Am. Chem. Soc.*, **2004**, 126 (22), 6864-6865; A. C. Atesin, J. Zhang, T. Vaidya, W. W. Brennessel, A. J. Frontier, R. Eisenberg, *Inorg. Chem.*, **2010**, 49 (9), 4331-4342.
- 145- R. Sanz, D. Miguel, F. Rodriguez, *Angew. Chemie. Int. Ed.*, **2008**, 120 (38), 7464-7467; R. Sanz, D. Miguel, M. Gohain, P. Garcia-Garcia, M. A. Fernandez-Rodriguez, A. Gonzalez-Perez, O. Nieto-Faza, A. R. de Lera, F. Rodriguez, *Chem. Eur. J.*, **2010**, 16 (32), 9818-9828.
- 146- I. Walz, A. Bertogg, A. Togni, *Eur. J. Org. Chem.*, **2007**, 2007 (16), 2650-2658.
- 147- A. P. Marcus, and R. Sarpong, *Org. Lett.*, **2010**, 12 (20), 4560-4563; A. P. Marcus, A. S. Lee, R. L. Davis, D. J. Tantillo, R. Sarpong, *Angew. Chem. Int. Ed.* **2008**, 47 (34), 6379-6383.
- 148- M. Kawatsura, Y. Higuchi, S. Hayase, M. Nanjo, T. Itoh, *Synlett*, **2008**, 7, 1009-1012.
- 149- J. A. Malona, J. M. Colbourne, A. J. Frontier, *Org. Lett.*, **2006**, 8, 5661-5664.

- 150- W. Guo-Peng, C. Meng-Qing, Z. Shou-Fei, Z. Qi-Lin, *Chem. Sci.*, **2017**, 8, 7197-7202.
- 151- (a) J. J. Turner, J. P. Healy, R. C. J. Dobson, J. A. Gerrard, C. A. Hutton, *Bioorg. Med. Chem. Lett.*, **2005**, 15 (4), 995-998; (b) B. A. Boughton, M. D. W. Griffin, P. A. O'Donnell, R. C. J. Dobson, M. A. Perugini, J. A. Gerrard, C. A. Hutton, *bioorg. Med. Chem.*, **2008**, 16 (23), 9975-9983.
- 152- C. J. Rieder, K. J. Winberg, F. G. West, *J. Am. Chem. Soc.*, **2009**, 131 (22), 7504-7505.
- 153- S. Lemaire-Audoire, and P. Vogel, *Tetrahedron: Asymmetry*, **1999**, 10 (7), 1283-1293.
- 154- G. Sudhakar, J. Raghavaiah, G. Mahesha, K. K. Singarapuc, *Org. Biomol. Chem.*, **2016**, 14, 2866-2872.
- 155- M. Shindo, K. Yaji, T. Kita, K. Shishido, *SYNLETT*, **2007**, 7, 1096-1100.
- 156- O. Diels, and K. Alder, *Justus Liebigs Ann. Chem.* **1928**, 460 (1), 98-122.
- 157- R. A. Carmichael, and W. A. Chalifoux, *Chem. Eur. J.* **2016**, 22 (26), 8781-8785.
- 158- H. Zheng, M. Lejkowski, D. G. Hall, *Tetrahedron Lett.*, **2013**, 54 (1), 91-94.
- 159- J. Sauer, *Angew. Chem. Int. Ed. Engl.*, **1967**, 6 (1), 16-33.
- 160- F. Fringuelli, and A. Taticchi, *The Diels-Alder Reaction: Selected Practical Methods*, Wiley, New York, **2002**.
- 161- J. Sauer and R. Sustmann, *Angew. Chemie., Int. Ed. Engl.* **1980**, 19 (10), 779-807.
- 162- R. B. Woodward, and R. Hoffmann, *Angew. Chemie. Int. Ed.*, **1969**, 8 (11), 781-853.

- 163- K. Fukui, *Acc. Chem. Res.* **1971**, 4 (2), 57-64.
- 164- K. N. Houk, *Acc. Chem. Res.* **1975**, 8 (11), 361-369.
- 165- R. B. Woodward and T. J. Katz, *Tetrahedron*, **1959**, 5, 70-89.
- 166- F. Fotiadu, F. Michel, G. Buono, *Tetrahedron Lett.* **1990**, 31 (34), 4863-4866.
- 167- B. Gaede and T. M. Balthazor, *J. Org. Chem.*, **1983**, 48 (2), 276-277.
- 168- W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, volume 8, 1st Edition, Pergamon Press, **1990**.
- 169- K. Alder, and H. G. Stein, *Angew. Chemie. Int. Ed.*, **1937**, 50 (28), 510-519.
- 170- J. G. Martin and R. K. Hill, *Chem. Rev.*, **1961**, 61 (6), 537-562.
- 171- J. Sauer, H. Wiest, A. Mielert, *Eur. J. Inorg. Chem.*, **1964**, 97 (11), 3183-3207.
- 172- H. Bruss, H. Schuster, R. Martinez, M. Kaiser, A. P. Antonchick, H. Waldmann, *Beilstein J. Org. Chem.*, **2014**, 10, 194-208; M. Kimura, M. Shimizu, S. Tanakab, Y. Tamaru, *Tetrahedron*, **2005**, 61, 3709-3718.
- 173- D. A. Smith, and K. N. Houk, *Tetrahedron Lett.*, **1991**, 32 (12), 1549-1552.
- 174- J. C. de Jong, F. Bolhuis, B. L. Feringa, *Tetrahedron: Asymmetry*, **1991**, 2 (12), 1247-1262.
- 175- R. K. Boeckman and D, M. Demko, *J. Org. Chem.*, **1982**, 47 (9), 1789-1792.
- 176- S. F. Martin, S. A. Williamson, Gist, R. P.; K. M. Smith, *J. Org. Chem.* **1983**, 48 (26), 5170-5180.
- 177- K. S. Anju, S. Ramakrishnan, A. P. Thomas, E. Suresh, A. Srinivasan, *Org. Lett.*, **2008**, 10 (24), 5545-5548.
- 178- A. Kabro, E. C. Escudero-Adán, V. V. Grushin, P. W. N. M. van Leeuwen, *Org. Lett.*, **2012**, 14 (15), 4014-4017; B. Yan-Jang, L. Shu-Ming, L. Ji-Tai, L. Tong-Shuang, *Ind. J. Chem.*, **2005**, 44B (8), 1720-1723.

- 179- D. J. Phillips, K. S. Pillinger, W. Li, A. E. Taylor, A. E. Graham, *Chem. Commun.*, **2006**, 0, 2280-2282.
- 180- A. Maiti and J. S. Yadav, *Synth. Commun.*, **2001**, 31 (10), 1499-1506.
- 181- R. J. K. Taylor, *Synthesis*, **1977**, 1977 (8), 564-565.
- 182- (a) C. J. O'Brien, F. Lavigne, E. E. Coyle, A. J. Holohan, B. J. Doonan, *Chem. Eur. J.*, **2013**, 19 (19), 5854-5858; (b) J. E. Rice, E. J. LaVoie, D. J. McCaustland, D. L. Fischer, J. C. W. Jr, *J. Org. Chem.*, **1986**, 51 (13), 2428-2434.
- 183- K. A. Runcie, and R. J. K. Taylor, *Chem. Commun.*, **2002**, 0, 974-975.
- 184- S. Beltrán-Rodil, M. G. Edwards, D. S. Pugh, M. Reid, R. J. K. Taylor, *Synlett*, **2010**, 4, 602-606.
- 185- E. D. Cox and J. M. Cook, *Chem. Rev.*, **1995**, 95 (6), 1797-1842.
- 186- Z. Yao, P. M. Krai, E. F. Merino, M. E. Simpso, C. Slebodnick, M. Belen Cassera, P. R. Carlier, *Bioorg. Med. Chem. Lett.*, **2015**, 25 (7), 1515-1519.
- 187- G. Tatsui, *Yakuga. Zasshi*, **1928**, 48, 91-94.
- 188- P. Campiglia, I. Gomez-Monterrey, T. Lama, E. Novellino, P. Grieco, *Molecular Diversity*, **2004**, 8 (4), 427-430.
- 189- (a) A. Pictet and T. Spengler, *Ber. Dtsch. Chem. Ges.*, **1911**, 44, 2030-2036; (b) G. J. Tatsui, *J. Pharm. Soc. Jpn.*, **1928**, 48, 92; For reviews of Pictet–Spengler reaction: (c) J. Stokigt, A.P. Antonchick, F. Wu and H. Waldmann, *Angew. Chemie., nt. Ed.*, **2011**, 50, 8538-8564.
- 190- N. Rashid, S. Alam, M. Hasan, N. Khan, K.M. Khan, H. Duddeck, G. Pescitelli, A. Kenéz, S. Antus, T. Kurtán, *Chirality*, **2012**, 24 (10), 789-795.
- 191- D. E. Scott, A. G. Coyne, A. Venkitaraman, T. L. Blundell, C. Abell, M. Hyvönen, *Chem. Med. Chem.*, **2015**, 10 (2), 296-303.

- 192- L. Samulis, and N. C.O. Tomkinson, *Tetrahedron*, **2011**, 67 (23), 4263-4267.
- 193- R. H. Dave, and B. D. Hosangad, *Tetrahedron*, **1999**, 55 (37), 11295-11308.
- 194- G. Massiot and T. Mulamba, *J. Chem. Soc. Chem. Commun.*, **1983**, 0, 1147-1149.
- 195- (a) K.L Rinehart, J. Kobayashi, G.C. Harbour, R.G. Hughes, S.A. Mizzsak, T.A. Scahill, *J. Am. Chem. Soc.* **1984**, 106 (5), 1524-1526. (b) R. Skouta, M. Hayano, K. Shimada, B.R. Stockwell, *Bioorg. Med. Chem. Lett.* **2012**, 22 (17), 5707-5713.
- 196- (a) L. S. Imlay, C. M. Armstrong, M. C. Masters, T. Li, K. E. Price, R. L. Edwards, K. M. Mann, L. X. Li, C. L. Stallings, N. G. Berry, P. M. O'Neill, A. R. Odom, *ACS Infect Dis.*, **2015**, 1 (4), 157-167; (b) L. V. Tunstall, PhD thesis, Synthesis and biological evaluation of three novel antimalarial series, Keele University, **2018**
- 197- (a) R. T. Arnold, S. T. Kulenovic, *J. Org. Chem.*, **1978**, 43 (19), 3687-3689; (b) Z. Y. LIANG, L. WANG, H. LIU, J. S. HUANG, *J. Chil. Chem. Soc.*, **2013**, 58 (1), 1558-1561.
- 198- T. G. Kyazimova, E. G. Mamedbeili, A. V. Nagiev, E. I. Suleimanova, Kh. S. Khalilov, *Russ. J. Appli. Chem.*, **2008**, 81 (10), 1803-1807.
- 199- T. R. Hoye, J. Jeon, L. C. Kopel, T. D. Ryba, M. A. Tennakoon, Y. Wang, *Angew. Chemie. Int. Ed.*, **2010**, 49 (35), 6151-6155.
- 200- W. H. Pecak, J. Son, A. J. Burnstine, L. L. Anderson, *Org. Lett.*, **2014**, 16 (13), 3440-3443.
- 201- A. Hassner and K. S. K. Murthy, A. Padwa, U. Chiacchio, D. C. Dean, A. M. Schoffstall, *J. Org. Chem.*, **1989**, 54 (22), 5277-5286.
- 202- V. Pace, L. Castoldi, A. D. Mamuye, W. Holzer, *SYNTHESIS*, **2014**, 46 (21), 2897-2909.

- 203- P. b. Landor, S. R. Landor, O. Odyek, *J. Chem. Soc., Perkin Trans I*, **1977**, 2, 93-95.
- 204- (a) S. Mukherjee, and B. List, *J. Am. Chem. Soc.*, **2007**, 129 (37), 11336-11337;
(b) G. B. Giovenzana, D. Imperio, A. Penoni, G. Palmisano, *Beilstein J. Org. Chem.*, **2011**, 7, 1095-1099.
- 205- M. Mori, and Y. Ban, *Chem. Pharm. Bull.*, **1976**, 24 (9), 1992-1999.
- 206- J. Mao, F. Liu, M. Wang, L. Wu, B. Zheng, S. Liu, J. Zhong, Q. Bian, P. J. Walsh, *J. Am. Chem. Soc.*, **2014**, 136 (50), 17662-17668.
- 207- J. MELNICK and S. M. WEINREB, *J. org. chem.*, **1988**, 53 (4), 850-854.
- 208- S. G. Tilve, R. E. Patre, S. Gawas, S. Sen, P. S. Parameswaranc, *Tetrahedron Lett.*, **2007**, 48 (20), 3517-3520.
- 209- (a) A. T. Bockus, K. W. Lexa, C. R. Pye, A. S. Kalgutkar, J. W. Gardner, K. C. R. Hund, W. M. Hewitt, J. A. Schwochert, E. Glassey, D. A. Price, A. M. Mathiowetz, S. Liras, M.P. Jacobson, R. S. Lokey, *J. Med. Chem.*, **2015**, 58 (11), 4581-4589; (b) H. Ming-Jie, X. De-Cai, Y. Xin-Shan, *Chem. Commun.*, **2012**, 48, 11079-11081.
- 210- (a) S. D. Burke, K. W. Jung, W. T. Lambert, J. R. Phillips, J. J. Klovning, *J. Org. Chem.*, **2000**, 65 (13), 4070-4087; (b) J. J. Kiddle, *Tetrahedron Lett.* **2000**, 41 (9), 1339-1341.
- 211- (a) P. Zhou, L. Huang, H. Jiang, A. Wang, X. Li, *J. Org. Chem.*, **2010**, 75 (23), 8279-8282; (b) E. Dolušić, P. Larrieu, S. Blanc, F. Sapunarić, B. Norberg, L. Moineaux, D. Colette, V. Stroobant, L. Pilotte, D. Colau, T. Ferain, *Bio. med. chem.* **2011**, 19 (4), 1550-1561.
- 212- (a) J. Basset, M. Romero, T. Serra, M. D. Pujol, *Tetrahedron*, **2012**, 68 (1), 356-362; (b) V. J. Alberto, L. Ehecát, I. M. Fabiola, E. Jiménez, C. M. del Carmen, C.

- P. Diana, U. R. Gutiérrez, D. Francisco; T. Joaquín, *ARKIVOV*, **2013**, 2014 (3), 18-
53.
- 213- A. Karadeolian and M. A. Kerr, *J. Org. Chem.*, **2010**, 75 (20), 6830-6841.
- 214- F. J. Sayago, M. J. Pueyo, M. I. Calaza, A. I. Jimenez, C. Cativiela, *Chirality*,
2011, 23 (7), 507-513.
- 215- A. S. Bourlot, E. Desarbre, J. Y. Mérour, *Synthesis*, **1994**, 1994 (4), 411-416.
- 216- M. L. Bennasar, T. Roca, F. Ferrando, *J. Org. Chem.*, **2005**, 70 (22), 9077-9080.
- 217- J. Roy and D. Mal, *Eur. J. Org. Chem.* **2014**, 2014 (9), 1873-1881.
- 218- D. S. Black, M. Santoso, K. Somphol, N. Kumar, *Tetrahedron*, **2009**, 65 (31),
5977-5983.
- 219- B. Schmidt, and N. Elizarov, *Chem. Commun.*, **2012**, 48, 4350-4352.
- 220- G. Deng, B. Xu, C. Liu, *Tetrahedron*, **2005**, 61 (24), 5818-5821.
- 221- M. Hussain, S. T. Toguem, R. Ahmad, D. T. Tung, I. Knepper, A. Villinger, P.
Langer, *Tetrahedron*, **2011**, 67 (29), 5304-5318.
- 222- S. Lemaire-Audoire and P. Vogel, *Tetrahedron: Asymmetry*, **1999**, 10 (7),
1283-1293.
- 223- T. G. Nikolaus, C. C. Răzvan, N. Van Der, J. H. Daan, E. Ruijter, O. V. Romano,
H. Mélanie, K. Faber, *Green Chemistry*, **2017**, 19 (2), 511-518.
- 224- T. Classen, M. Korpak, M. Schölzel, J. Pietruszka, *ACS Catal.*, **2014**, 5 (4),
1321-1331.
- 225- P. K. Shyam, C. Lee, J. Hye-Young, *Bulletin of the Korean Chemical Society*,
2015, 36 (7), 1824-1827.
- 226- J. Fang, J. Jian, H. Chang, T. Kuo, W. Lee, P. Wu, H. Wu, *Eur. Chem. J.*, **2017**,
23 (8), 1830-1838.

- 227- R. M. Archer, M. Hutchby, C. L. Winn, J. S. Fossey, S. D. Bull, *Tetrahedron*, **2015**, 71 (46), 8838-8847.
- 228- T. Jiang, K. Huynh, T. Livinghouse, *Synlett*, **2013**, 24 (02), 193-196.
- 229- E. Krawczyk, M. Koprówski, K. Łuczak, *Tetrahedron: Asymmetry*, **2007**, 18 (15), 1780-1787.
- 230- H. S. Pawar, A. S. Wagha, A. M. Lali, *New J. Chem.*, **2016**, 40 (6), 4962-4968.
- 231- H. S. Pawar, A. S. Wagha, A. M. Lali, *J. Name.*, **2013**, 0, 1-3.